THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

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 and Deletion/Duplication Panels include analysis of the 79 genes listed below.

Microcephaly Sequencing Panel						
Congenital Microcephaly					Postnatal Microcephaly	
Syndromic			Autosomal Recessive Primary Microcephaly			
ARFGEF2	KIAA1279	PQBP1	AGMO	PHC1	CDKL5	TRAPPC9
ASXL3	KIF11	QARS	ASPM	SASS6	DYRK1A	TSEN2
ATR	LIG4	RBBP8	CASC5	STIL	FOXG1	TSEN34
ATRX	NBN	SLC25A19	CDK5RAP2	WDR62	MECP2	TSEN54
CASK	NDE1	SOX11	CDK6	ZNF335	MED17	UBE3A
CDC6	NHEJ1	SPATA5	CENPE		PYCR2	
CDT1	NIN	STAMBP	CENPF		RAB18	
CEP63	ORC1	TRMT10A	CENPJ		RAB3GAP1	
CTNNB1	ORC4	TUBGCP4	CEP135		RAB3GAP2	
DIAPH1	ORC6	TUBGCP6	CEP152		SLC1A4	
EIF2S3	PCNT	USP18	CIT		SLC2A1	
EFTUD2	PLK4	WWOX	CRIPT		SLC9A6	
IER3IP1	PNKP	ZEB2	MCPH1		TBC1D20	
KATNB1	PPP1R15B		MFSD2A		TCF4	

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	*De novo* 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 *de novo 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.
CDC6 [OMIM#602627] *CDT1* [OMIM#605525] *ORC1* [OMIM#601902] *ORC4* [OMIM#603056] *ORC6* [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 *ORC1* have been identified in 4/33 individuals with MGS (8). Mutation analysis of other genes of this pre-replication complex showed mutations in *ORC4, ORC6, CDT1 and CDC6* in 14 individuals from nine families with MGS (9). Guernsey *et al* identified mutations in *ORC1, ORC4* and *CDT1* 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.
CEP63 [OMIM#614728]	AR	A homozygous nonsense mutation was identified in *CEP63* 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).
CTNNB1 [OMIM# 615075]	AD	Mutations in the CTNNB1 gene are associated with autosomal dominant intellectual disability. Approximately half of all affected individuals have primary microcephaly (11)
DIAPH1 [OMIM# 602121]	AR	Biallelic mutations in *DIAPH1* are associated with seizures, cortical blindness and microcephaly syndrome [OMIM# 616632]. Homozygous loss-of-function mutations in the *DIAPH1* gene have been reported in three consanguineous families with early-onset seizures, microcephaly, cortical visual impairment, short stature and developmental delay (12, 13).
EFTUD2 [OMIM# 610536]	AD	The *EFTUD2* gene is associated with mandibulofacial dysostosis and progressive (14). Microcephaly is typically present at birth and progresses to -3 to 6- SD over time.
EIF2S3 [OMIM# 300161]	XL	Hemizygous mutations in the *EIF2S3* gene have been identified in two unrelated families where affected males presented with severe intellectual disability, microcephaly, growth retardation and epilepsy (15).
IER3IP1 [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 (16).
KATNB1 [OMIM# 616212]	AR	Homozygous mutations in *KATNB1* have been identified in multiple unrelated consanguineous families with microcephaly and variable brain malformations in cortical development, including lissencephaly, pachygyria, and hypoplasia of the corpus callosum (17).
KIAA1279 [OMIM# 609367]	AR	Goldberg-Shprintzen syndrome (GOSHS) is an autosomal recessive multiple malformation disorder characterized by microcephaly, Hirschsprung megacolon, hypertelorism, submucous cleft palate, short stature, and intellectual disability (18).
KIF11 [OMIM#148760]	AD	Ostergaard *et al.* (2012) identified *KIF11* mutations in individuals from 17 families with autosomal dominant microcephaly and primary lymphedema [OMIM#152950] and/or chorioretinopathy [OMIM#156590] (19). Most individuals had mild to moderate intellectual disabilities. Nonsense, splice site, missense, and frameshift mutations were all observed.
LIG4 [OMIM#601837]	AR	Biallelic truncating *LIG4* mutations have been identified in a series of 11 patients with microcephalic primordial dwarfism (20). The position of truncating mutations has been observed to correlate with phenotypic severity (20). *LIG4* mutations have been recurrently reported in LIG4 syndrome (OMIM#606593), originally identified in a typically-developing 14-year-old with acute lymphoblastic leukemia (21). Bone marrow failure has occurred in 70% of patients reported to date (20). Other patients with LIG4 syndrome are described as having immunodeficiency, developmental delay, Seckel or "bird-like" facies, microcephaly, and growth restriction (22).
MED17 [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 (23).
NDE1 [OMIM#609449]	AR	Mutations in *NDE1* have been reported in children with severe congenital microcephaly, with brains smaller than 10 SD below the mean, simplified gyri, and profound intellectual disability (24). Homozygous mutations have been reported in one Turkish, two Saudi and two Pakistani consanguineous families.
NBN (NBS1) [OMIM#602667]	AR	*Nibrin* (abbreviation *NBN*, previously *NBS1*) is mutated in Nijmegen breakage syndrome, an autosomal recessive disorder characterized by microcephaly, intellectual disability, growth restriction, immunodeficiency, and predisposition to cancer (25). The majority of

		patients are homozygous for the common deletion mutation 657del5. Other frameshift as well as nonsense mutations have been reported.
NIN [OMIM#608064]	AR	Compound heterozygous missense mutations have been identified in the *NIN* gene in two sisters with Seckel syndrome 7 (26).
NHEJ1 [OMIM#611290]	AR	Buck *et al.* (2006) identified *NHEJ1* mutations in patients with congenital microcephaly, growth restriction, dysmorphia (bird-like face), and immunodeficiency as well as variable bone and kidney abnormalities (27). Mutations observed included missense, nonsense, frameshift/splice site (in *cis*), and in-frame deletions.
PCNT [OMIM#605925]	AR	Mutations in *PCNT* 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 (28). Rauch et al. (2008) identified 29 different homozygous or compound heterozygous mutations in the *PCNT* gene in 25 patients with MOPD2 (28).
PLK4 [OMIM# 616171]	AR	*PLK4* mutations have been reported in families with features of primoridal dwarfism, including severe primary microcephaly and growth retardation (29). Patients can have ocular abnormalities including microphthalmia, microcornea, and cataracts.
PNKP [OMIM #605610]	AR	Mutations in the *PNKP* 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 (30).
PPP1R15B [OMIM# 613257]	AR	Bilallelic mutations in *PP1R15B* have been reported in two unrelated consanguineous families presenting with microcephaly, short stature and intellectual disability with or without insulin-dependent diabetes mellitus and/or identified CNS abnormalities (31, 32).
PQBP1 [OMIM# 300463]	X-linked	The *PQBP1* gene is associated with Renpenning syndrome, and X-linked disorder characterized by intellectual disability, microcephaly, short stature, spastic paraplegia and midline defects in affected males (33).
QARS [OMIM# 603727]	AR	Individuals with biallelic mutations in the QARS gene have congenital progressive microcephaly, cerebral and cerebellar atrophy, and onset of intractable seizures in infancy (34).
RBBP8 [OMIM#604124]	AR	A homozygous splicing mutation in *RBBP8* was identified in four siblings affected by Seckel syndrome [OMIM#606744] in a consanguineous Iraqi family (35). 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).
SLC25A19 [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 SLC25A19 (36).
SOX11 [OMIM# 600898]	AD	Hempel et al. reported ten individuals with a mild Coffin-Siris syndrome-like phenotype, but without a classical phenotype permitting a clinical diagnosis of CSS. Seven of these patients were found to have chromosome 2p25 deletions encompassing SOX11, and three had de novo *SOX11* mutations. In-vivo studies by the same group support a role for *SOX11* in neurodevelopment (37).
SPATA5 [OMIM# 613940]	AR	Tanaka et al. identified biallelic mutations in *SPATA5* in ten families and fourteen individuals with microcephaly, developmental delay, intellectual disability, hypotonia, spasticity, seizures, sensorineural hearing loss, and cortical visual impairment (38).
STAMBP [OMIM#606247]	AR	McDonnell et al. identified mutations in *STAMBP* 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 quardriparesis, hypoplastic distal phalanges and poor growth (39).
TRMT10A [OMIM#616013]	AR	Homozygous nonsense and missense mutations in *TRMT10A* have been identified in two consanguineous families with multiple children with microcephaly, intellectual disability, short stature, delayed puberty, seizures, and disturbed glucose metabolism (40, 41).
TUBGCP4 [OMIM# 609610]	AR	Biallelic mutations in *TUBGCP4* are associated with congenital microcephaly and chorioretinal dysplasia (42).
TUBGCP6 [OMIM#610053]	AR	In a Mennonite infant with primary microcephaly and chorioretinopathy, a homozygous missense mutation was identified in *TUBGCP6* (43). The carrier frequency among Old Order Amish and Mennonite was estimated at 2% (identified in 2/202 individuals).
USP18 [OMIM# 607057]	AR	Loss-of-function recessive mutations in *USP18* were identified in five patients from two unrelated families, all of who has Pseudo-TORCH syndrome (PTS). PTS is characterized by microcephaly, enlarged ventricles, cerebral calcification and occasional systemic features at birth resembling congenital infection, but with no identified cause

		(44).
WWOX [OMIM# 616211]	AR	Biallelic mutations in *WWOX* are associated with progressive microcephaly, early infantile epileptic encephalopathy and retinopathy (45).
ZEB2 [OMIM#605802]	AD	Mutations in *ZEB2* are associated with Mowat-Wilson syndrome (MWS) [OMIM # 235730], which is characterized by distinctive facial features, moderate-to-severe mental retardation, microcephaly and seizures (46). 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 (46).

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 (47).

***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
AGMO [OMIM#613738]	AR	Novel homozygous mutations in *AGMO* were identified in a consanguineous Saudi Arabian family with two children affected with primary microcephaly, developmental delay, short stature and intellectual disability (48).
ASPM [OMIM#605481]	AR	Mutations in the *ASPM* gene are the most common cause of autosomal recessive primary microcephaly (49). Approximately 40% of patients with a strict diagnosis of MCPH have mutations in *ASPM*. However, fewer patients (<10%) with a less restrictive phenotype have mutations in *ASPM* (50).
CASC5 [OMIM#609173]	AR	Genin *et al.* (2012) identified the same *CASC5* frameshift mutation in the homozygous state in three separate consanguineous families with autosomal recessive primary microcephaly (51).
CDK5RAP2 [OMIM #608201]	AR	Homozygous mutations in *CDK5RAP2* have been identified in three Pakistani families with autosomal recessive primary microcephaly (52, 53).
CDK6 [OMIM#603368]	AR	Homozygous missense mutations in *CDK6* were identified in a large Pakistani family with 10 individuals presenting with microcephaly (-4 SD to -6SD), sloping foreheads, and mild intellectual disability (54).
CENPE [OMIM# 117143]	AR	Compound heterozygous mutations in *CENPE* have been described in one family with affected siblings with primary microcephaly, short stature, and severe developmental delays (55). Brain imaging showed simplified gyral pattern, partial agenesis of the corpus callosum and cerebellar hypoplasia.
CENPF [OMIM# 600236]	AR	Truncating mutations in *CENPF* have been reported on one family with an affected child with autosomal recessive primary microcephaly (56).
CENPJ [OMIM #609279]	AR	Four Pakistani families with autosomal recessive primary microcephaly have been reported with homozygous mutations in *CENPJ (53, 57)*.
CEP135 [OMIM#614673]	AR	Hussain *et al.* identified a homozygous frameshift mutation in *CEP135* in a consanguineous family with two siblings affected by autosomal recessive primary microcephaly (58).
CEP152 [OMIM #613529]	AR	Homozygous or compound heterozygous mutations in the *CEP152* gene were identified in 3 unrelated Canadian families with MCPH (59).
CIT [OMIM# 605629]	AR	Homozygous missense mutations in the *CIT* gene have been identified in three consanguineous families affected with autosomal recessive primary microcephaly, and in three unrelated families with multiple affected children affected by severe microlissencephaly (60, 61).
MCPH1 [OMIM #607117]	AR	Homozygous mutations in *MCPH1* have been reported in multiple populations, including at least one Pakistani family and at least one Caucasian family (62-64).
MFSD2A [OMIM# 614397]	AR	Homozygous mutations in *MFSD2A* have been identified in at least three consanguineous families with autosomal recessive primary microcephaly (65).
PHC1 [OMIM#602978]	AR	A homozygous missense *PHC1* 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 (66).
SASS6 [OMIM# 616402]	AR	One family with autosomal recessive primary microcephaly and a homozygous missense mutation in *SASS6* has been reported (67).
STIL [OMIM #181590]	AR	Kumar *et al* (2009) reported three Indian families with autosomal recessive primary microcephaly and homozygous mutations in *STIL* (68).
WDR62 [OMIM#613583]	AR	Mutations in *WDR62* 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 (69). Homozygous missense and frameshift mutations were first reported in seven consanguineous families (70).
ZNF335 [OMIM#610827]	AR	Yang *et al.* (2012) identified a homozygous mutation in *ZNF335* in a large consanguineous Arab-Israeli family with severe autosomal recessive primary microcephaly (71).

Postnatal Microcephaly Genes

Gene	Inheritance	Clinical Features
CDKL5 [OMIM#300203]	XL	*CDKL5* 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 (72). 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 (72).
DYRK1A [OMIM#60085]	AD	The *DYRK1A* 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 (73). Both *DYRK1A* mutations (74) and deletions (73) have been identified in patients with microcephaly and intellectual disability. Mutations in *DYRK1A* are typically *de novo*.
FOXG1 [OMIM#164874]	AD	Abnormalities of the *FOXG1* gene have been identified in patients with the congenital variant of Rett syndrome [OMIM#613454] (75). Patients with *FOXG1* mutations typically have early onset epilepsy, severe cognitive impairment, progressive postnatal microcephaly, postnatal growth deficiency and dyskinetic movement disorders (75). Unlike classic Rett syndrome there is typically no observed period of normal development prior to onset of symptoms (75).
MECP2 [OMIM#300005]	XL	*MECP2* mutations are present in 70-90% of females with classic Rett syndrome [OMIM#312750] and approximately 20% of females with atypical Rett syndrome (76). 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 (76). *MECP2* mutations appear to be more common in females than in males, and the majority of cases are *de novo* (76). There have been reports of unaffected or mildly affected *MECP2* carrier females due to skewed X inactivation.
MED17 [OMIM#603810]	AR	A homozygous missense mutation in *MED17* was identified in 5 infants from 4 Jewish families with postnatal progressive microcephaly with seizures and brain atrophy [OMIM#613668] (23).
RAB18 [OMIM#602207] *RAB3GAP1* [OMIM#602536] *RAB3GAP2* [OMIM#609275] *TBC1D20* [OMIM #611663]	AR	Mutations in *RAB18, RAB3GAP1, RAB3GAP2,* and *TBC1D20* are associated with Warburg Micro syndrome [OMIM#600118], which is characterized by ocular and neurodevelopmental abnormalities and hypothalamic hypogonadism (77-79). Key clinical features include microcephaly, microphthalmia, microcornia, congenital cataracts, optic atrophy, cortical dysplasia and atrophy, congenital hypotonia, severe intellectual disability, and spastic diplegia (77). 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 (77).
PYCR2 [OMIM# 616406]	AR	Biallelic mutations in *PYCR2* are associated with hypomyelinating leukodystrophy, postnatal progressive microcephaly, and severe developmental delays (80).
SLC1A4 [OMIM# 600229]	AR	A study by Damseh et al. identified eleven Ashkenazi Jewish patients from eight families with progressive microcephaly and developmental delay. 9 of the 11 patients were homozygous for the c.766G>A, p.E256K mutation, while the remaining two had alternate biallelic mutations in *SLC1A4*. Among 860 unaffected Ashkenazi Jewish individuals, six carried the p.E256K mutation, leading to a carrier rate estimate of 1/144 in this population (81, 82).
SLC2A1 [OMIM#138140]	AD	Glucose transporter-1 (GLUT-1) deficiency syndrome [OMIM#612126] is caused by mutations in the *SLC2A1* 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 (83). A ketogenic diet is effective in mitigating clinical findings in affected individuals.
SLC9A6 [OMIM#300231]	XL	Mutations in the *SLC9A6* gene have been identified in patients with X-linked Angelman-like syndrome [OMIM#300243] (84). Features of males with *SLC9A6* mutations include progressive microcephaly, grand mal epilepsy, lack of speech, trunal ataxia, excessive drooling, and a happy demeanor with spontaneous smiling and laughter (84). Mutations

		in *SLC9A6* result in clinical features in affected males and occasionally some mild features in carrier females (84).
TCF4 [OMIM#602272]	AD	Mutations in *TCF4* 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 (85). Other common features include acquired microcephaly, epilepsy, hyperventilation episodes, short stature, stereotypic hand movements, and absent speech (85).
TRAPPC9 [OMIM#611966]	AR	Marangi *et al*. (2013) concluded that the phenotype associated with loss-of-function mutations in the *TRAPPC9* gene is recognizable and can be characterized by dysmorphic facial appearance, obesity, hypotonia, moderate to severe intellectual disability, and consistent brain abnormalities (86). *Trappc9* is highly expressed in the mouse brain (87). All mutations reported to date have been homozygous and protein truncating.
TSEN2 [OMIM#608753] *TSEN34* [OMIM#608755] *TSEN54* [OMIM#608755]	AR	Mutations in *TSEN2, TSEN34* and *TSEN54* 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 (88). Significant microcephaly develops after birth (88). MRI findings include a small cerebellum and brainstem, variable neocortical atrophy, severe and progressive microcephaly and variable ventriculomegaly (89). Clinically, most patients have severe intellectual disability, swallowing problems, and seizures (89).
UBE3A [OMIM#601623]	AD	Mutations in *UBE3A* 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 (90). Other characteristics noted in over 80% of patients include microcephaly, seizures, and a specific, abnormal EEG pattern (90). Most mutations in *UBE3A* are *de novo*, with a <1% recurrence rate, however some cases may be familial (90).

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.

Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Microcephaly Sequencing Panel (79 genes)*

Sample specifications:	3 to10 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.

Microcephaly Deletion/Duplication Panel (79 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2500
CPT codes:	81407
Turn-around time:	6 weeks

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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