THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Molecular Testing for Lissencephaly

Clinical Features:

Classic Lissencephaly (LIS) or Lissencephaly Type 1 is a smooth or nearly smooth cerebral surface caused by deficient neuronal migration. The spectrum of malformations ranges from complete agyria (absent gyri) to regional pachygyria to subcortical band heterotopia (SBH).

- Lissencephaly—"smooth brain" with absent (agyria) or abnormally wide gyri (pachygyria)
- SBH—"double cortex"; band of heterotopic gray matter below the cortex separated by a thin zone of normal white matter
- Miller-Dieker syndrome—lissencephaly, characteristic facial features and severe neurologic abnormalities
- X-linked lissencephaly with abnormal genitalia (XLAG)—lissencephaly and moderately increased thickness of the cortex, absence of the corpus callosum, infantile spasms, hypothalamic dysfunction including deficient temperature regulation, and ambiguous genitalia in males.

Lissencephaly and SBH are classified by anterior-posterior gradient and severity. This classification may help determine the best order for genetic testing.

Dr. William Dobyns at the Seattle Children's Research Institute is available to review MRI scans and give recommendations regarding genetic testing. Please contact Dr. Dobyns (wbd@uw.edu) to arrange this, if desired.

Our Lissencephaly Panel includes mutation analysis of all 45 genes listed below.

Lissencephaly Panel				
ACTB	CRADD	ISPD	PIK3R2	SRD5A3
ACTG1	DAG1	KATNB1	POMGNT1	TMEM5
ARX	DCX	KIF5C	POMGNT2	TMTC3
ATP6V0A2	DMRTA2	LAMA2	POMK	TUBA1A
B3GALNT2	DYNC1H1	LAMB1	POMT1	TUBB
B3GNT1	FKRP	LARGE	POMT2	TUBB2B
CDK5	FKTN	NDE1	RELN	TUBB3
CIT	GMPPB	PAFAH1B1	RTTN	TUBG1
COL3A1	GPR56	PHGDH	SNAP29	VLDLR

Molecular Genetics:

The genetic causes of lissencephaly are complex, and may result from abnormalities in one of the genes below:

Gene / Condition	Inheritance Pattern	Clinical Features and Molecular Pathology
ACTB ACTG1	AD	Baraitser-Winter syndrome is a developmental disorder characterized by congenital ptosis, high-arched eyebrows, hypertelorism, ocular colobomata and anterior-predominant lissencephaly. Other features include postnatal short stature, microcephaly, ID, seizures and hearing loss[1]. Mutations in both *ACTB* and *ACTG1*, which code for cytoplasmic actin, have been identified in patients with Baraitser-Winter syndrome.
ARX	X-linked	*ARX* mutations cause various phenotypes including XLAG, X-linked infantile spasms, and non-syndromic X-linked mental retardation[2-4]. Females with more severe mutations may be affected as well, and have agenesis of the corpus callosum and seizures[5].
ATP6V0A2	AR	Homozygous or compound heterozygous mutations in the *ATP6V0A2* gene cause autosomal recessive cutis laxa type IIA (ARCL2A). This condition is characterized by overfolding and wrinkling of the skin and dysmorphic craniofacial features. Individuals with ARCL2A have early developmental delays, and seizures associated with a neurodegenerative course[6]. Van Maldergem *et al.* (2008) reported cortical malformations reminiscent of Walker-Warburg syndrome in 8 patients with ARCL2A[6].

B3GALNT2 *B3GNT1* *DAG1* *FKTN* *FKRP* *GMPPB* *LARGE* *POMGNT1* *POMGNT2* *POMK* *POMT1* *POMT2* *ISPD* *TMEM5*	AR	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies type A (MDDGA) is a genetically heterogeneous group of autosomal recessive conditions caused by defective glycosylation of DAG1, including Walker-Warburg syndrome, muscle-eye-brain and Fukuyama muscular dystrophy. Features of these conditions include brain and eye malformations, cognitive impairment, and congenital muscular dystrophy. Brain malformations seen in MDDGA include cobblestone lissencephaly, polymicrogyria, hydrocephalus, and cerebellar hypoplasia. Cobblestone lissencephaly (COB, previously designated as lissencephaly "type 2"), is a brain malformation consisting of a complex cortical dysplasia with glioneuronal heterotopia on the brain surface, moderate to severe lissencephaly, dysmyelination, hypoplastic brainstem, and dysplastic cerebellum with cysts. Mutations in *FKTN, FKRP, LARGE, POMGnT1, POMT1* and *POMT2* account for approximately 32-50% of patients with cobblestone lissencephaly[7]. Mutations in *TMEM5* and *ISPD* account for approximately 20% of patients with cobblestone lissencephaly[8].
CDK5	AR	In a consanguineous family with individuals affected by severe lissencephaly, cerebellar hypoplasia and agenesis of the corpus callosum, Magen *et al* (2015) identified a homozygous truncating variant in the *CDK5* gene[9].
CIT	AR	Biallelic mutations in the *CIT* gene have been reported in individuals with severe congenital microcephaly, and variable abnormalities on brain MRI including lissencephaly, simplified gyral pattern, and cerebellar/brainstem hypoplasia[10,11].
COL3A1	AR	Biallelic variants in *COL3A1* have been described in individuals with a cobblestone-like cortical malformation on brain MRI, white matter changes and cerebellar dysplasia. Additional findings may include developmental delay, easy bruising, arterial dissections and joint hypermobility[12].
CRADD	AR	A "thin" lissencephaly variant characterized by megalencephaly, frontal predominant pachygyria, intellectual disability, and seizures has been described in patients with biallelic mutations in the *CRADD* gene[13].
DCX	X-linked	*DCX* abnormalities result in severe lissencephaly or SBH in boys, but a less severe SBH in girls[14]. *DCX* abnormalities are generally associated with an a>p gradient. In males, *DCX* mutations are present in approximately 30% with SBH and approximately 10% with lissencephaly. In females, *DCX* mutations are present in approximately 80% with SBH, especially those with diffuse bands or bilateral frontal only bands. Intragenic deletions of the *DCX* gene are present in approximately 10% of female patients with SBH in whom no mutations were identified by *DCX* sequencing[15,16].
DYNC1H1	AD	Heterozyogous mutations in *DYNC1H1* are associated with cortical malformations including pachygyria, polymicrogyria and nodular heterotopia[17].
DMRTA2	AR	A homozygous truncating variant in *DMRTA2* has been described in affected individuals from a consanguineous family with a severe prenatal neurodevelopmental disorder characterized by fronto-parietal pachygyria/ lissencephaly, agenesis of the corpus callosum and progressive severe microcephaly[18].
GPR56	AR	Biallelic mutations in *GPR56* have been associated with a range of phenotypes, from bilateral bifrontoparietal polymicrogyria, to cobblestone-like lissencephaly[19].
KATNB1	AR	Homozygous mutations in *KATNB1* have been identified in multiple unrelated consanguineous families with variable malformations in cortical development, including lissencephaly, pachygyria, and hypoplasia of the corpus callosum[20].
KIF5C	AD	Heterozygous mutations in *KIF5C* have been associated with severe cortical malformations including gyral simplification and polymicrogyria[17].
LAMA2	AR	*LAMA2*-related muscular dystrophy is an autosomal recessive group of conditions ranging from late-onset proximal weakness and motor delays to profound neonatal hypotonia, failure to thrive, ophthalmoparesis, and respiratory failure. A small proportion of individuals with early-onset *LAMA2*-related muscular dystrophy have brain malformations, including pachygyria and cortical dysplasia[21]. The majority of affected individuals have normal cognitive abilities and cognitive development is not consistently correlated with brain MRI findings[22].
LAMB1	AR	In two consanguineous families with cobblestone lissencephaly, Radmanesh *et al* (2013) identified two different homozygous loss-of-function mutations in the *LAMB1* gene[23]. Radmanesh et al. noted that although the brain malformations were similar to those identified in patients with muscular-dystrophy-dystroglycanopathies, these patients did not have significant eye or muscle disease.
NDE1	AR	Mutations in *NDE1* have been reported in children with severe congenital microcephaly, with brains smaller than 10 SD below the mean, with simplified gyri, and profound developmental handicap with normal body growth. Patients may also have lissencephaly or microhydraencephaly. Paciorkowski, *et al.* (2013) reported a patient with a full gene deletion and a truncating mutation in *NDE1* who had severe microcephaly, agenesis of the corpus callosum, and a cortical dysplasia with a polymicrogyria-like appearance[24.] NDE1 is highly expressed in the developing human and mouse cerebral cortex, particularly at the centrosome, and has a role in mitotic spindle assembly during early

		neurogenesis. Deficiency of NDE1 therefore appears to cause failure of neurogenesis and a deficiency of cortical lamination.
PAFAH1B1 (LIS1)	AD	*PAFAH1B1 (LIS1)* abnormalities cause the most severe form of lissencephaly and are generally associated with a p>a gradient[25]. *PAFAH1B1* mutations are present in approximately 30% of patients with *PAFAH1B1*-related lissencephaly and rarely in patients with SBH. Microdeletions involving 17p13.3 are present in 100% of patients with MDS and approximately 50% of patients with lissencephaly. Intragenic deletions of one or more exons of *LIS1* are present in approximately 15% of patients with *PAFAH1B1*-related lissencephaly[26].
PHGDH	AR	Biallelic mutations in the *PHGDH* gene have been reported in individuals with Neu-Laxova Syndrome 1 (NLS-1) and PHGDH deficiency[27,28]. PHGDH deficiency is a serine biosynthesis disorder characterized by reduced L-serine concentrations, congenital microcephaly, intractable seizures and delayed psychomotor development. Neu-Laxova Syndrome 1 is a multiple congenital anomaly syndrome characterized by intrauterine fetal growth restriction, reduced fetal mobility, distinctive facial features, skeletal/limb malformations, icthyosis, brain developmental abnormalities (including microcephlay, lissencepahly, hypoplastic cerebellum, absent cerebellum vermis, etc) and perinatal lethality. It has been hypothesized that NLS represents the severe end of the spectrum for the serine metabolism deficiency[28,29].
PIK3R2	AD	Heterozygous mutations in the *PIK3R2* gene have been identified in patients with megalencephaly related overgrowth disorder called as megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 1(MPPH)[30]. The reported spectrum of brain malformations includes megalencephaly, perisylvian polymicrogyria, mega corpus callosum, cerebellar tonsillar ectopia (Chiari 1 malformation), hydrocephalus and dysmyelination. Other characteristic features are absence of vascular malformations, postaxial polydactyly, abnormal muscle tone, spasticity, epilepsy, mild dysmorphic features, developmental delays and intellectual disability[30-32]. Mosaic variants have also been described in patients with these phenotypes[33]. *Our sequencing assay is designed to detect germline variants; variants present in the mosaic state may not be detected by this assay.*
RELN *VLDLR*	AR	*RELN* mutations have been identified in patients with a less severe form of lissencephaly with cerebellar hypoplasia (LCH)[34]. *VLDLR*-associated cerebellar hypoplasia (*VLDLR*-CH) falls within the LCH spectrum, and is characterized by non-progressive congenital ataxia, ID, dysarthria, strabismus and seizures. These patients have mild lissencephaly as well. *VLDR* is part of the reelin (*RELN*) signaling pathway, which guides neuroblast migration in the cerebral cortex and cerebellum. LCH is distinguished from *VLDLR*-CH by more severe lissencephaly with an a>p gradient, a small and malformed hippocampus, and profound cerebellar hypoplasia with complete absence of detectable folia[35].
RTTN	AR	Kheradmand Kia *et al* (2012) identified a homozygous mutation in *RTTN* in three members of a consanguineous family with polymicrogyria and seizures[36]. The polymicrogyria in these affected individuals was asymmetric, extending from the frontal lobes to the temporal, parietal and occipital lobes on brain MRI. The RTTN protein is required for the early development of left-right specification and axial rotation and may play a role in notochord development.
SNAP29	AR	Sprecher *et al* (2005) identified a homozygous truncating mutation in two unrelated consanguineous Arab Muslim families with cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma (CEDNIK) syndrome. Individuals with CEDNIK syndrome have progressive microcephaly in conjunction with a range of brain malformations, including cortical dysplasia, pachygyria, absence of the corpus callosum, and perisylvian polymicrogyria. Additional features include dysmorphic facies, palmoplantar keratosis and ichthyosis, severe developmental delays, optic disc hypoplasia, and sensorineural hearing loss[37].
SRD5A3	AR	Mutations in *SRD5A3* are associated with congenital disorder of glycosylation type Iq (CDG1Q). CDG1Q is a rare autosomal recessive condition characterized by abnormal type 1 glycosylation in association with congenital eye malformations including ocular colobomas and optic disc hypoplasia, intellectual disabilities, and variable brain malformations. Al-Gazali *et al.* (2008) reported a consanguineous family with multiple affected individuals. Brain malformations seen in affected individuals included cerebellar vermis hypoplasia, hypoplasia of the corpus callosum, absent septum pellucidum, and bilateral frontal polymicrogyria[38]. Cantagrel *et al.* (2010) subsequently identified a homozygous mutation in *SRD5A3* in affected individuals in this family, as well as homozygous or compound heterozygous *SRD5A3* mutations in 5 other individuals[39].
TMTC3	AR	Jerber *et al*. (2016) identified biallelic mutations in *TMTC3* in six unrelated consanguineous families with cobblestone lissencephaly and other brain malformations such as ventriculomegaly, brainstem and cerebellar hypoplasia. Other most commonly reported features are delayed psychomotor development with truncal hypotonia, variable

		appendicular spasticity, intellectual disability and seizures. Only a minority of patients presented with ocular defects or elevated muscle creatine phosphokinase (CPK) which are one of the prominent features of other known congenital dystroglycanopathies[40].
TUBA1A	AD	*TUBA1A* mutations have been identified in patients with gyral malformations and are associated with two forms of lissencephaly. The first is lissencephaly with a p>a gradient similar to *LIS1*-associated lissencephaly, although this is rare cause of typical lissencephaly. The second is a severe form of lissencephaly associated with severe cerebellar hypoplasia (LCH) and often underdevelopment of the corpus callosum. About 30-40% of children with LCH have mutations in *TUBA1A*[41].
TUBB *TUBB3*	AD	Pathogenic variants in *TUBB* (previously known as *TUBB5*) and *TUBB3* have been associated with cortical malformations including simplified gyral patterns[42].
TUBB2B	AD	*De novo* mutations in the *TUBB2B* gene have been associated with a range of cortical malformations, including polymicrogyria and lissencephaly[43].
TUBG1	AD	Heterozygous mutations in *TUBG1* have been associated with moderate to severe lissenencephaly and subcortical band heterotopia[42].

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.

Lissencephaly Panel (36 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$4000
CPT codes:	81406, 81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Cobblestone Lissencephaly panel (21 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2500
CPT codes:	81406 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.

References

1. Rivière JB, van Bon BW, Hoischen A, et al. De novo mutations in the actin genes ACTB and ACTG1 cause Baraitser-Winter syndrome. *Nat Genet.* 2012;44(4):440-444, S441-442.
2. Kitamura K, Yanazawa M, Sugiyama N, et al. Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat Genet.* 2002;32(3):359-369.
3. Bienvenu T, Poirier K, Friocourt G, et al. ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. *Hum Mol Genet.* 2002;11(8):981-991.
4. Strømme P, Mangelsdorf ME, Shaw MA, et al. Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy. *Nat Genet.* 2002;30(4):441-445.

5. Marsh E, Fulp C, Gomez E, et al. Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females. *Brain.* 2009;132(Pt 6):1563-1576.
6. Van Maldergem L, Yuksel-Apak M, Kayserili H, et al. Cobblestone-like brain dysgenesis and altered glycosylation in congenital cutis laxa, Debre type. *Neurology.* 2008;71(20):1602-1608.
7. Devisme L, Bouchet C, Gonzalès M, et al. Cobblestone lissencephaly: neuropathological subtypes and correlations with genes of dystroglycanopathies. *Brain.* 2012;135(Pt 2):469-482.
8. Vuillaumier-Barrot S, Bouchet-Séraphin C, Chelbi M, et al. Identification of mutations in TMEM5 and ISPD as a cause of severe cobblestone lissencephaly. *Am J Hum Genet.* 2012;91(6):1135-1143.
9. Magen D, Ofir A, Berger L, et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with a loss-of-function mutation in CDK5. *Hum Genet.* 2015;134(3):305-314.
10. Harding BN, Moccia A, Drunat S, et al. Mutations in Citron Kinase Cause Recessive Microlissencephaly with Multinucleated Neurons. *Am J Hum Genet.* 2016.
11. Shaheen R, Hashem A, Abdel-Salam GM, Al-Fadhli F, Ewida N, Alkuraya FS. Mutations in CIT, encoding citron rho-interacting serine/threonine kinase, cause severe primary microcephaly in humans. *Hum Genet.* 2016;135(10):1191-1197.
12. Vandervore L, Stouffs K, Tanyalçin I, et al. Bi-allelic variants in. *J Med Genet.* 2017;54(6):432-440.
13. Di Donato N, Jean YY, Maga AM, et al. Mutations in CRADD Result in Reduced Caspase-2-Mediated Neuronal Apoptosis and Cause Megalencephaly with a Rare Lissencephaly Variant. *Am J Hum Genet.* 2016;99(5):1117-1129.
14. des Portes V, Pinard JM, Billuart P, et al. A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. *Cell.* 1998;92(1):51-61.
15. Matsumoto N, Leventer RJ, Kuc JA, et al. Mutation analysis of the DCX gene and genotype/phenotype correlation in subcortical band heterotopia. *Eur J Hum Genet.* 2001;9(1):5-12.
16. Hehr U, Uyanik G, Aigner L, Couillard-Despres S, Winkler J. DCX-Related Disorders. In: Pagon R, Bird T, Dolan C, eds. *GeneReviews [Internet]*. Seattle: University of Washington; 2007.
17. Poirier K, Lebrun N, Broix L, et al. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nat Genet.* 2013;45(8):962.
18. Urquhart JE, Beaman G, Byers H, et al. DMRTA2 (DMRT5) is mutated in a novel cortical brain malformation. *Clin Genet.* 2016;89(6):724-727.
19. Bahi-Buisson N, Poirier K, Boddaert N, et al. GPR56-related bilateral frontoparietal polymicrogyria: further evidence for an overlap with the cobblestone complex. *Brain.* 2010;133(11):3194-3209.
20. Mishra-Gorur K, Çağlayan AO, Schaffer AE, et al. Mutations in KATNB1 cause complex cerebral malformations by disrupting asymmetrically dividing neural progenitors. *Neuron.* 2014;84(6):1226-1239.
21. Quijano-Roy S, Sparks S, Rutkowski A. LAMA2-Related Muscular Dystrophy. In: Pagon R, Bird T, Dolan C, eds. *GeneReviews [Internet].* Seattle: University of Washington; 2012.
22. Messina S, Bruno C, Moroni I, et al. Congenital muscular dystrophies with cognitive impairment. A population study. *Neurology.* 2010;75(10):898-903.
23. Radmanesh F, Caglayan AO, Silhavy JL, et al. Mutations in LAMB1 cause cobblestone brain malformation without muscular or ocular abnormalities. *Am J Hum Genet.* 2013;92(3):468-474.
24. Paciorkowski AR, Keppler-Noreuil K, Robinson L, et al. Deletion 16p13.11 uncovers NDE1 mutations on the non-deleted homolog and extends the spectrum of severe microcephaly to include fetal brain disruption. *Am J Med Genet A.* 2013;161A(7):1523-1530.
25. Lo Nigro C, Chong CS, Smith AC, Dobyns WB, Carrozzo R, Ledbetter DH. Point mutations and an intragenic deletion in LIS1, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrome. *Hum Mol Genet.* 1997;6(2):157-164.
26. Dobyns W, Das S. LIS1-Associated Lissencephaly/Subcortical Band Heterotopia. In: Pagon R, Bird T, Dolan C, eds. *GeneReviews [Internet]*. Seattle: University of Washington; 2009.
27. Tabatabaie L, de Koning TJ, Geboers AJ, van den Berg IE, Berger R, Klomp LW. Novel mutations in 3-phosphoglycerate dehydrogenase (PHGDH) are distributed throughout the protein and result in altered enzyme kinetics. *Hum Mutat.* 2009;30(5):749-756.
28. Shaheen R, Rahbeeni Z, Alhashem A, et al. Neu-Laxova syndrome, an inborn error of serine metabolism, is caused by mutations in PHGDH. *Am J Hum Genet.* 2014;94(6):898-904.
29. Acuna-Hidalgo R, Schanze D, Kariminejad A, et al. Neu-Laxova syndrome is a heterogeneous metabolic disorder caused by defects in enzymes of the L-serine biosynthesis pathway. *Am J Hum Genet.* 2014;95(3):285-293.
30. Rivière JB, Mirzaa GM, O'Roak BJ, et al. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nat Genet.* 2012;44(8):934-940.
31. Nakamura K, Kato M, Tohyama J, et al. AKT3 and PIK3R2 mutations in two patients with megalencephaly-related syndromes: MCAP and MPPH. *Clin Genet.* 2014;85(4):396-398.
32. Terrone G, Voisin N, Abdullah Alfaiz A, et al. De novo PIK3R2 variant causes polymicrogyria, corpus callosum hyperplasia and focal cortical dysplasia. *Eur J Hum Genet.* 2016;24(9):1359-1362.
33. Mirzaa GM, Conti V, Timms AE, et al. Characterisation of mutations of the phosphoinositide-3-kinase regulatory subunit, PIK3R2, in perisylvian polymicrogyria: a next-generation sequencing study. *Lancet Neurol.* 2015;14(12):1182-1195.
34. Hong SE, Shugart YY, Huang DT, et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. *Nat Genet.* 2000;26(1):93-96.
35. Boycott K, Parboosingh J. VLDLR-Associated Cerebellar Hypoplasia. In: Pagon R, Bird T, Dolan C, eds. *GeneReviews [Internet]*. Seattle: University of Washington; 2008.
36. Kheradmand Kia S, Verbeek E, Engelen E, et al. RTTN mutations link primary cilia function to organization of the human cerebral cortex. *Am J Hum Genet.* 2012;91(3):533-540.

37. Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M, et al. A mutation in SNAP29, coding for a SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma. *Am J Hum Genet.* 2005;77(2):242-251.
38. Al-Gazali L, Hertecant J, Algawi K, El Teraifi H, Dattani M. A new autosomal recessive syndrome of ocular colobomas, ichthyosis, brain malformations and endocrine abnormalities in an inbred Emirati family. *Am J Med Genet A.* 2008;146A(7):813-819.
39. Cantagrel V, Lefeber DJ, Ng BG, et al. SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. *Cell.* 2010;142(2):203-217.
40. Jerber J, Zaki MS, Al-Aama JY, et al. Biallelic Mutations in TMTC3, Encoding a Transmembrane and TPR-Containing Protein, Lead to Cobblestone Lissencephaly. *Am J Hum Genet.* 2016;99(5):1181-1189.
41. Poirier K, Keays DA, Francis F, et al. Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (TUBA1A). *Hum Mutat.* 2007;28(11):1055-1064.
42. Bahi-Buisson N, Poirier K, Fourniol F, et al. The wide spectrum of tubulinopathies: what are the key features for the diagnosis? *Brain.* 2014;137(Pt 6):1676-1700.
43. Fallet-Bianco C, Laquerrière A, Poirier K, et al. Mutations in tubulin genes are frequent causes of various foetal malformations of cortical development including microlissencephaly. *Acta Neuropathol Commun.* 2014;2:69.

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