THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Early Infantile Epileptic Encephalopathy Panel

Clinical Features and Molecular Genetics:

Early infantile epileptic encephalopathy (EIEE), also known as Ohtahara syndrome, is a severe form of epilepsy characterized by frequent tonic spasms with onset in the first months of life. EEG reveals suppression-burst patterns, characterized by high-voltage bursts alternating with almost flat suppression phases. Seizures are medically intractable with evolution to West syndrome at 3-6 months of age and then Lennox-Gastaut syndrome at 1-3 years of age. EIEE represents approximately 1% of all epilepsies occuring in children less than 15 years of age (1). Patients have severe developmental delay and poor prognosis. The diagnostic workup of EIEEs remains challenging because of frequent difficulties in defining etiologies. Acquired structural abnormalities like hypoxic-ischemic insults and isolated cortical malformations, which represent the most common causes of epileptic encelphalopathy in infancy should be excluded first (2).

Our EIEE Panel includes analysis of all 60 genes listed below

Early Infantile Epileptic Encephalopathy Panel				
AARS	CHD2	GNAO1	PLCB1	SLC25A22
ALDH7A1	CLCN4	GRIN2A	PNKP	SLC2A1
ALG13	DNM1	GRIN2B	PNPO	SPTAN1
ARFGEF2	DOCK7	HCN1	POLG	ST3GAL3
ARHGEF9	DYRK1A	ITPA	SCN1A	ST3GAL5
ARV1	EEF1A2	KCNA2	SCN2A	STXBP1
ARX	EFHC1	KCNB1	SCN8A	SYNGAP1
BRAT1	ETHE1	KCNH5	SIK1	SZT2
CACNA1A	FGF12	KCNQ2	SLC1A2	TBC1D24
CACNA2D2	FRRS1L	KCNT1	SLC1A4	WDR45
CASK	GABRA1	NECAP1	SLC12A5	WWOX
CDKL5	GABRB3	PCDH19	SLC13A5	

Gene	Inheritance	Clinical Features and Molecular Pathology
AARS [OMIM#601065]	AR	Biallelic mutations in *AARS* have been reported in two siblings and one unrelated individual with EIEE. In-vitro studies showed that both mutations identified resulted in loss of AARS function (3)
ALG13 [OMIM#300776]	XL	A hemizygous *de novo* mutation in *ALG13* was identified by Timal *et al.* (2012) in a male patient with a congenital disorder of glycosylation, microcephaly, seizures, and death at one year of age (4). The Epi4K Consortium identified a *de novo* mutation in *ALG13* in two female patients with infantile spasms and developmental delays (5). Both patients exhibited hypsarrhythmia on EEG.
ALDH7A1 [OMIM#107323]	AR	Mutations in *ALDH7A1* are associated with pyridoxine-dependent epilepsy (PDE), which is characterized by EIEE that is resistant to antiepileptic drugs but responsive to large doses of pyridoxine (vitamin B6) (6).
ARFGEF2 [OMIM#605371]	AR	Homozygous splice-site mutations in the ubiquitously expressed *ARFGEF2* gene were identified in a consanguineous Pakistani kindred with multiple children who presented with West syndrome, evolving to Lennox–Gastaut syndrome with severe intellectual disability, microcephaly and associated with diffuse periventricular heterotopia (7).
ARHGEF9 [OMIM#300607]	XL	Shimojima *et al.* (2011) identified a nonsense mutation in *ARHGEF9* in one out of 23 males with severe intellectual disability and epilepsy (8). A missense mutation in *ARHGEF9* in a male with severe intellectual disability, hyperekplexia (excessive startle) and refractory infantile-onset epilepsy has also previously been described (9).
ARV1 [OMIM#611647]	AR	Homozygous splice site and missense mutations in *ARV1* have been identified in two consanguineous families with children affected by EIEE. Transfection of the mutations into

		HEK cells resulted in no detectable protein levels, and functional studies were consistent with a loss of function effect of the mutations (12, 13)
ARX [OMIM#300382]	XL	Up to 10% of males with a clinical diagnosis of EIEE or West syndrome/cryptogenic infantile spasms may have mutations in the *ARX* gene (1, 14). Carrier females of *ARX* mutations can be asymptomatic (15).
BRAT1 [OMIM#614506]	AR	Several studies have identified homozygous or compound heterozygous mutations in the *BRAT1* gene in patients with a neonatal lethal form of rigidity and multifocal seizure syndrome, including a founder mutation in the Amish population (16-18). Horn, *et al*, described two brothers who were compound heterozygotes for *BRAT1* mutations, with EIEE and a milder phenotype and survival into childhood ((19).
CACNA1A [OMIM#601011]	AD	Pathogenic mutations in *CACNA1A* were identified in five probands and one sibling with early-onset epileptic encephalopathy (5, 20). Of the 6 infants with *CACNA1A* mutations, five began having seizures on the first day of life, with the affected siblings additionally showing seizure-like movements in utero. Multiple seizure types were present in all affected individuals, as well as developmental delay.
CACNA2D2 [OMIM#607082]	AR	Edvardson *et al.* (2013) identified a homozygous missense mutation in *CACNA2D2* in three affected siblings from a consanguineous family (21). An unaffected sibling was a carrier of the mutation. Seizures onset in the affected individuals was at 20-60 days of life. Seizures were refractory to treatment and included atonic, clonic, and tonic seizures. Functional studies demonstrated dysfunction of the α2 omega2 subunit of high voltage gated calcium channels, resulting in reduced current density and slow inactivation in neuronal calcium channels (21).
CASK [OMIM#300172]	XL	Hemizygous loss of function mutations in the *CASK* gene were identified by Saitsu *et al.* (2012) in two males with Ohtahara syndrome. One patient had a *de novo* nonsense mutation and the other had a deletion involving exon 2 that was maternally inherited from a mother with somatic mosaicism for the deletion (22).
CDKL5 [OMIM#300203]	XL	Archer *et al.* (2006) identified *CDKL5* mutations in 7/42 (17%) of females with severe mental retardation and seizures in the first 6 months of life (23). The most common feature found in patients reported to date with *CDKL5* mutations is the early onset of seizures. *CDKL5* mutations have been reported in more female than male patients, however, Elia, *et al* (2008) reported *CDKL5* mutations in 3/8 boys with severe mental retardation and early-onset seizures (24).
CHD2 [OMIM#602119]	AD	In a cohort of 500 patients with epileptic encephalopathy, 1.2% were found to have *de novo* mutations in CHD2 (25). Reported features include: Dravet syndrome (26), myoclonic seizures, absence seizures, photosensitivity, and moderate to severe intellectual disability (25). Mutations leading to protein truncation, as well as missense mutations have been reported.
CLCN4 [OMIM#302910]	XL	In a group of children with difficult to control epilepsy and developmental delay, Veeramah *et al* (2013) found a single patient with a hemizygous *de novo* missense mutation in *CLNC4* (10). In addition to epilepsy, this child had microcephaly, hypotonia, myotonia, and intellectual disability.
DNM1 [OMIM#602377]	AD	Heterozygous mutations in *DNM1* are associated with EIEE-31. The EuroEPINOMICS-RES Consortium *et al.* (2014) reported 5 unrelated patients with EIEE who were found to have *de novo* heterozygous mutations in *DNM1* (27). All patients were reportedly normal at birth and developed treatment-resistant seizures between 2 and 13 months of age. Three of the five patients had developmental delays prior to seizure onset, and all patients exhibited severe to profound intellectual disabilities at the time of evaluation (27).
DOCK7 [OMIM#615730]	AR	Perrault, *et al.* (2014) identified compound heterozygous nonsense mutations in *DOCK7* in two siblings with early-onset intractable epilepsy, global developmental delays and intellectual disabilities, and cortical blindness (28). The patients exhibited dysmorphic features including low anterior hairline, telecanthus, and broad nasal tip with anteverted nares. An unrelated patient with seizures starting at 5 months of age, profound developmental delays, and cortical blindness was subsequently found to also be a compound heterozygote for two nonsense mutations in *DOCK7* (28).
EEF1A2 [OMIM#602959]	AD	In 2012, de Ligt *et al.* identified a *de novo* missense mutation in a patient with a history of neonatal hypotonia and seizures at 4 months with intellectual disability, autistic features, and aggressive behavior (29). Subsequently, in a group of children with difficult to control epilepsy and developmental delay, Veeramah *et al* (2013) found a single patient with a *de novo* missense mutation in *EEF1A2* (10).
EFHC1 [OMIM#608815]	AD/AR	Berger *et al.* (2012) described a family with primary intractable epilepsy in infancy with a homozygous missense mutation in *EFHC1* (30). The affected children died at 18-36 months of age. Heterozygous mutations in *EFHC1* have been associated with increased susceptibility to junvenile myoclonic epilepsy (31).

ETHE1 [OMIM#608451]	AR	Homozygous or compound heterozygous mutations in *ETHE1* are associated with ethylmalonic encephalopathy, a rare metabolic disorder characterized by neurodevelopmental regression and progressive pyramidal findings, seizures, petechiae, and death typically occurring in the first decade of life. Papetti *et al.* (2015) reported a patient who presented with epileptic encephalopathy at 3 months of life. By 5 months of age the patient's EEG findings had progressed to West syndrome (32). The patient later developed petechiae, developmental regression, and pyramidal signs. This patient was found to have a truncating variant in *ETHE1* on the paternal allele and two missense variants on the maternal *ETHE1* allele. ETHE1 protein was absent on Western blot analysis. This is the first report of a patient with ETHE1 mutations and an early pure epileptic onset (32).
FHF1 (FGF12) [OMIM#601513]	AD	Siekierska *et al.* (2016) reported a *de novo* heterozygous missense mutation in the *FHF1* gene in two siblings affected by a lethal disorder consisting of EIEE and progressive cerebellar atrophy. Further functional studies support a gain of function phenotype, and studies in zebrafish enhanced epileptiform discharges in larval-stage animals (33).
FRRS1L [OMIM#604574]	AR	Four different homozygous mutations in the *FRRS1L* gene were identified in eight patients from four unrelated families with EIEE. Functional studies in fibroblasts showed reduced FRRS1L protein levels, and mouse models indicated that FRSS1L is expressed throughout the brain (34). Affected members of another consanguineous family with EIEE were also found to have a homozygous mutation in the *FRRS1L* gene (35)
GABRA1 [OMIM#137160]	AD	Carvill, *et al.* (2014) identified heterozygous, *de novo* missense mutations in four *SCN1A*-negative patients with Dravet syndrome (36). Patients had onset of seizures between 8 and 11 months of age. Multiple seizure types were observed, including absence, focal dyscognitive, hemiclonic, myoclonic, tonic-clonic, and status epilepticus. All patients had mild to moderate developmental delays (36). Heterozygous mutations in *GABRA1* have previously been associated with susceptibility to familial juvenile myoclonic epilepsy and generalized epilepsy (37, 38).
GABRB3 [OMIM#137192]	AD	The Epi4K Consortium identified heterozygous *de novo GABRB3* mutations in four unrelated patients with epileptic encephalopathy. Three of the reported patients had a Lennox-Gastaut syndrome phenotype; the fourth had infantile spasms (5).
GNAO1 [OMIM#139311]	AD	Nakamura *et al.* (2013) identified *de novo* mutations in four individuals with EIEE, three of whom were described as having Ohtahara syndrome, and two of whom had involuntary movements (39). One of the patients had somatic mosaicism, with only one third to half of various cell types harboring the mutation. Missense mutations and a small in-frame deletion were reported.
GRIN2A [OMIM#613971]	AD	Endele *et al.* (2010) found heterozygous *GRIN2A* mutations in two out of 127 individuals with a history of idiopathic epilepsy and/or abnormal EEG findings and a variable degree of intellectual disability (40). The most consistent clinical feature seen in individuals with *GRIN2A* mutations is epilepsy, which varies in severity between individuals. The most severe cases are associated with EIEE (40).
GRIN2B [OMIM#138252]	AD	Lemke *et al.* (2014) identified *de novo* heterozygous missense mutations in *GRIN2B* in three unrelated individuals with early epileptic encephalopathy/West syndrome (41). The affected individuals had severe developmental delays and onset of focal epilepsy in early infancy. *GRIN2B* encodes the beta subunit of the glutamate-activated N-methyl-D-aspartate (NMDA) receptor. Two of the *GRIN2B* mutations were introduced into *Xenopus laevis* oocytes and functional studies revealed dramatically increased Ca^{2+} permeability, consistent with a gain of function effect of these mutations (41).
HCN1 [OMIM#602780]	AD	Nava *et al.* (2014) identified heterozygous mutations in *HCN1* in six unrelated patients with EIEE (42). The mutation was confirmed to be *de novo* in five of the six patients. Seizure onset ranged from 4 to 13 months. Seizures seen in affected individuals included febrile, tonic-clonic, clonic, absence, focal, and myoclonic. Patients exhibited mild to severe intellectual disabilities and the majority of patients also had behavioral concerns. Two of the patients also exhibited ataxia. Functional studies of the confirmed *de novo* mutations in Chinese hamster ovary cells indicated gain-of-function in three of the five mutations and a possible dominant negative effect in the remaining two *de novo* cases (42).
ITPA [OMIM#616647]	AR	Kevelam *et al.* (2015) identified biallelic loss of function mutations in *ITPA* in seven patients from four families. The patients presented with EIEE and brain abnormalities noted on MRI, microcephaly, variable cardiac defects and early death. ITPase activity in erythrocytes and fibroblasts was severely reduced in patient cell lines when compared to controls (43)
KCNA2 [OMIM#176262]	AD	Syrbe *et al.* (2015) identified *de novo* heterozygous mutations in *KCNA2* in 7 unrelated patients with severe early onset epilepsy. Onset of seizures occurred between 5 and 17 months of age, and remission of seizures occurred in childhood or adolescence for 4 patients. All patients exhibited normal development prior to onset of seizures but had

		neurologic deficits after onset of epilepsy (44). In vitro functional assays in *Xenopus laevis* revealed that some mutations had dominant negative effect and other mutations led to gain of function (44).
KCNB1 [OMIM#600397]	AD	Torkamani *et al.* (2014) identified *de novo* heterozygous missense mutations in 3 unrelated patients with early onset epileptic encephalopathy and difficult to control seizures. All patients exhibited developmental delays (45).
KCNH5 [OMIM#605716]	AD	In a group of children with difficult to control epilepsy and developmental delay, Veeramah *et al.* (2013) found a single patient, whose presentation was consistent with West syndrome, with a *de novo* heterozygous mutation in *KCNH5* (10).
KCNQ2 [OMIM#602235]	AD	Weckhuysen *et al.* (2012) identified heterozygous *KCNQ2* mutations in 8 out of 80 patients with EIEE, 6 of which were confirmed to be *de novo.* Mutations in *KCNQ2* can also be associated with other phenotypes including benign familial neonatal seizures (BFNS), which is an autosomal dominant seizure disorder typically associated with a good prognosis (46). Parental mosaicism has been described in one family with a mutation in *KCNQ2* (46, 47).
KCNT1 [OMIM#608167]	AD	Barcia *et al*. (2012) identified *de novo* heterozygous gain-of-function mutations in *KCNT1* in six patients with a subtype of EIEE known as malignant migrating partial seizures of infancy (48). Missense mutations in *KCNT1* have also been reported in families with autosomal dominant nocturnal frontal lobe epilepsy-5 (49)
NECAP1 [OMIM#611623]	AR	A homozygous nonsense mutation in *NECAP1* was identified by Alazami *et al.* (2014) in multiple individuals with EIEE from a consanguineous family (50). The affected individuals exhibited decreased fetal movement, hypotonia and poor feeding. Severe intractable seizures developed in affected individuals in early infancy. Two of the affected individuals underwent brain MRI and were found to have generalized brain atrophy (50).
PCDH19 [OMIM#300088]	XL	Mutations in the *PCDH19* gene have been associated with EIEE. Marini et al. (2010) identified 13 different mutations in the PCDH19 gene in 13 (11%) of 117 female patients with febrile seizures and a wide spectrum of epilepsy phenotypes (51). *PCDH19* mutations are X-linked, with the phenotype being restricted to females. Males with hemizygous mutations are apparently unaffected with normal cognitive functions. This unusual mode of inheritance is likely to be due to cellular interference, a mechanism assuming that only the co-existence of PCDH19 positive and negative cells, as a result of random X inactivation in females, is pathogenic (23).
PLCB1 [OMIM#607120]	AR	Kurian et al. (2010) identified a homozygous deletion of the promoter element and exons 1-3 of the *PLCB1* gene in a child with EIEE from a consanguineous family of Bangladeshi descent.
PNKP [OMIM#613402]	AR	Mutations in the *PNKP* gene are associated with early-onset intractable epilepsy, microcephaly, developmental delay and behavioral abnormalities (52). Missense and frameshift mutations identified in PNKP have been associated with severe encephalopathy, whereas an intronic deletion identified in one individual, that was predicted to disrupt proper mRNA splicing, was associated with a milder phenotype (52, 53). The PNKP protein is involved in DNA repair of both double and single-stranded breaks, however at this time no features typically associated with DNA repair defects, such as cancer predisposition or immunological abnormalities have been reported in affected individuals (52).
PNPO [OMIM#603287]	AR	Mills et al (2005) found homozygous mutations in PNPO in 3 individuals with early infantile epileptic encephalopathy and biochemical changes in the CSF, indicative of reduced activity of aromatic L-amino acid decarboxylase (AADC) (54). This was found to be due to deficiency of pyridoxal phosphate (PLP), which is a co-factor of AADC and is synthesized by the enzyme encoded for by the PNPO gene. Of the 3 affected children, only one was treated with PLP and survived the neonatal period, however he continued to have symptoms such as seizures, severe developmental delays and dystonic spasms (54).
POLG [OMIM#174763]	AR	In a study of 213 children with early or juvenile onset nonsyndromic intractable epilepsy, Uusimaa *et al.* (2013) identified 5 (2.3%) with compound heterozygous or homozygous mutations in the *POLG* gene (55). The majority of patients had elevated cerebrospinal fluid lactate. A proportion of affected individuals may develop liver failure, particularly if their seizures are being treated with sodium valproate (55).
SCN1A [OMIM#607208]	AD	Mutations in the *SCN1A* gene can cause EIEE6, which is more commonly known as Dravet syndrome. EIEE6 is characterized by onset of seizures in the first year of life, often triggered by fever, photostimulation, or modest hyperthermia, which usually evolve to include myoclonic seizures over time (56). Mutations in *SCN1A* associated with EIEE6 are typically *de novo* (1). Of those with a clinical diagnosis of EIEE6, 85% have a mutation in *SCN1A* (56).
SCN2A [OMIM#182390]	AD	Ogiwara *et al.* (2009) identified 2 *de novo* mutations in the *SCN2A* gene in a cohort of 116 patients with intractable childhood epilepsies (57). Mutations in the *SCN2A* gene can also

		cause benign familial neonatal seizures (BFNS).
SCN8A [OMIM#600702]	AD	Veeramah *et al.* (2012) identified a *de novo* mutation in *SCN8A* in a female with EIEE (58). Symptoms started at 6 months of age with refractory generalized seizures, and the patient died suddenly at age 15 years (58).
SIK1 [OMIM#616341]	AD	Hansen *et al.* (2015) identified different *de novo* heterozygous mutations in *SIK1 in* 6 unrelated children with early-onset epilepsy. Seizures began shortly after birth in all patients, along with severely delayed psychomotor development. Two patients died in infancy, while the remaining four had significant cognitive impairment and EEG abnormalities (59)
SLC1A2 [OMIM#600300]	AD	*De novo* mutations in *SLC1A2* have been reported in three female patients with early-onset epileptic encephalopathies (5, 20). These infants had a severe epilepsy phenotype characterized by seizure onset in the first week of life and profound developmental impairment. All three individuals had multiple seizure types with prominent myoclonic and tonic seizures as well as spasms.
SLC1A4 [OMIM#600229]	AR	Homozygous and compound heterozygous mutations in *SLC1A4* have been associated with a condition predominantly found in the Ashkenazi Jewish population, consisting of microcephaly, severe developmental delay, neuroimaging abnormalities, and seizures. The majority of reported patients have been found to be homozygous for a founder mutation, p.Glu256Lys A report by Conroy *et al.* (2016) described a patient of European descent born to consanguineous parents, who presented with an early-onset seizure disorder with infantile spasms, focal motor, and focal dyscognitive seizures. The patient was found to be heterozygous for a nonsense mutation in the *SLC1A4* gene. This finding suggests that truncating mutations may cause a more severe seizure and developmental phenotype than the previously described Ashkenazi Jewish patients (60)
SLC12A5 [OMIM#616645]	AR	Biallelic mutations in *SLC12A5* were identified In four children from two families with EIEE. The children presented with infantile-onset focal migrating seizures, neurological regression and developmental delay. In vitro studies showed that the mutations negatively impact expression and glycosylation of the potassium-chloride co-transporter KCC2, which resulting in impaired synaptic inhibition (61).
SLC13A5 [OMIM#608305]	AR	Homozygous or compound heterozygous mutations in *SLC13A5* are associated with EIEE25 (62, 63). Affected individuals develop seizures in the first week of life. Other features seen in affected individuals include ataxia, choreoathetosis, spasticity, and microcephaly. Some affected individuals also were found to have tooth hypoplasia or hypodontia (63).
SLC25A22 [OMIM#609302]	AR	Homozygous mutations in *SLC25A22* have been described in case reports of consanguineous families with EIEE (57, 64).
SLC2A1 [OMIM#606777]	AD	Glucose transporter-1 (GLUT1) deficiency syndrome is caused by heterozygous 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, developmental delay, acquired microcephaly, hypotonia, spasticity, ataxia and dystonia (64). Seizures are typically refractory and worsen during periods of fasting (65). The majority of reported cases are due to *de novo* mutations (66).
SPTAN1 [OMIM#182810]	AD	Saitsu *et al* (2010) identified de-novo heterozygous mutations in 2 unrelated Japanese patients with EIEE (67).
ST3GAL3 [OMIM#606494]	AR	A homozygous mutation in *ST3GAL3* was identified in a consanguineous Palestinian family with four individuals affected by severe early infantile epileptic encephalopathy (68). Mutations in *ST3GAL3* have also been described in patients with mild to moderate non-syndromic intellectual disability (68).
ST3GAL5 [OMIM#604402]	AR	Mutations in *ST3GAL5* are associated with infantile onset of refractory and recurrent seizures, associated with profoundly delayed psychomotor development, abnormal movements, and vision loss (69). A founder mutation is present in the Amish community (69). A homozygous mutation was also found in an affected child of French ancestry.
STXBP1 [OMIM#602926]	AD	Sequencing of STXBP1 detected mutations in 4 out of 106 patients with EIEE (70). Earlier reports identified 4 heterozygous missense mutations in 13 patients with EIEE(71). Parental mosaicism has been described in one family with a mutation in STXBP1 (46, 47).
SYNGAP1 [OMIM#603384]	AD	Carvill *et al.* (2013) identified heterozygous *de novo* nonsense mutations in two unrelated individuals with epileptic encephalopathy with seizure onset in infancy. Three additional patients were found to have truncating mutations in *SYNGAP1* but parents were not available in these cases to confirm the *de novo* nature of the variants (25). All patients exhibited developmental delays prior to seizure onset. Multiple seizure types were observed, including absence, atypical absence, focal dyscognitive, tonic-clonic, and myoclonic seizures (25).
SZT2	AR	In 2 unrelated patients with EIEE, Basel-Vanagaite et al. (2013) identified biallelic

[OMIM#615463]		truncating mutations in the SZT2 gene (72). The phenotype was characterized by lack of psychomotor development apparent from birth, dysmorphic facial features, early onset of refractory seizures, and thick corpus callosum and persistent cavum septum pellucidum on brain imaging.
TBC1D24 [OMIM#613577]	AR	Homozygous or compound heterozygous mutations in *TBC1D24* are associated with EIEE16 (73). Affected individuals develop seizures in the first weeks or months of life. Seizures are frequent and unresponsive to medication. Affected infants exhibit developmental regression or lack of developmental progress. Most affected individuals die in childhood (73, 74). Mutations in *TBC1D24* can also cause familial infantile myoclonic epilepsy, a less severe seizure disorder (75).
WDR45 [OMIM#300526]	XLD	Pathogenic mutations in WDR45 are known to be associated with neurodegeneration with brain iron accumulation (NBIA), primarily affecting females. However, three male patients and one affected female sibling with West syndrome were found to have hemizygous *WDR45* mutations. Their clinical features included early-onset seizures, developmental delay and intellectual disability. In two of the male patients, the mutations were *de novo*, with a somatic mutation identified in the mother of the affected siblings (76).
WWOX [OMIM#605131]	AR	Abdel-Salam *et al.* (2014) identified a homozygous mutation in *WWOX* in a patient with severe, early onset seizures, microcephaly, growth retardation, lack of psychomotor development, optic atrophy, and death at 16 months of age (77). Mignot *et al.* (2015) subsequently identified 5 patients from 4 families with EIEE. Affected individuals had profound developmental delays, microcephaly, hypotonia, and progressive cerebral atrophy (78).

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. 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.

Our Epilepsy Exome Panel is also available (see website). In addition, mutation analysis of individual genes is offered separately for several of the genes on the EIEE panel, including *ARX, CDKL5, PCDH19, PNKP, STXBP1, SLC25A22* and *SPTAN1.* Please see our website for more details regarding these other test options.

EIEE Panel (59 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 EIEE panel

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire EIEE panel. All abnormal results are reported by telephone or email.

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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