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PCDH19 Analysis for X-linked Female-Limited Epilepsy with Mental Retardation

Clinical Features:

X-linked Female-limited Epilepsy with Mental retardation (EFMR, OMIM#300088) is characterized by seizure onset in infancy or early childhood (6-36 months) and cognitive impairment. Seizures are predominantly generalized, including tonic-clonic, myoclonic, tonic and atonic seizures. The spectrum of phenotypes has been extended to include female patients with early onset epileptic encephalopathies resembling Dravet syndrome or focal epilepsy with or without mental retardation (1).

Molecular Genetics

EFMR is caused by mutations in *PCDH19* (protocadherin 19; OMIM#300460), located at Xq22. Protocadherins form a subfamily of calcium-dependent cell-cell adhesion molecules in the cadherin superfamily, and *PCDH19* has been found to be expressed in the central nervous system, including the hippocampus and cortex, suggesting a role in cognitive function. 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 (2). Gross and partial deletions of *PCDH19* have also been reported (3).

Inheritance:

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 (3).

Test methods:

We offer full gene sequencing for all 5 coding exons and the intron/exon boundaries of *PCDH19* by direct sequencing of amplification products in both the forward and reverse directions. Deletion/duplication analysis 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. *PCDH19* sequencing and deletion/duplication analysis is also offered as part of our Early Infantile Epileptic Encephalopathy Panel (see website for more details).

PCDH19 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1150
CPT codes:	81404
Turn-around time:	4 – 6 weeks

PCDH19 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81403
Turn-around time:	4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 weeks

Deletion/duplication analysis for two or more genes (by array-CGH)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	$1545
CPT codes:	81479
Turn-around time:	4-6 weeks

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. Additional reports are available as requested. All abnormal results are reported by telephone.

References:

1. Specchio N, Marini C, Terracciano A et al. Spectrum of phenotypes in female patients with epilepsy due to protocadherin 19 mutations. Epilepsia 2011: 52: 1251-1257.
2. Marini C, Mei D, Parmeggiani L et al. Protocadherin 19 mutations in girls with infantile-onset epilepsy. Neurology 2010: 75: 646-653.
3. Depienne C, Trouillard O, Bouteiller D et al. Mutations and deletions in PCDH19 account for various familial or isolated epilepsies in females. Hum Mutat 2011: 32: E1959-1975.

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