

Courtagen's epiSEEK®



Epilepsy

epiSEEK® Comprehensive Sequence Analysis for Epilepsy and Seizure Disorders (327 gene panel)

Introduction:

Courtagen's epiSEEK® test provides the complete Next Generation Sequencing of 327 genes that have been reported in association with epileptic phenotypes. This panel addresses a broad clinical spectrum of syndromic and nonsyndromic epileptic presentations.

The epiSEEK® test is validated on saliva and blood samples.

For a complete list of the genes included in this panel, as well as descriptions and phenotype associations, please visit www.courtagen.com.

- **Glycosylation Disorders (23 genes)**
- **Mitochondrial Dysfunction (27 genes)**
- **Idiopathic Generalized Epilepsy (28 genes)**
- **Early Infantile Encephalopathy (16 genes)**
- **Neurodegeneration (32 genes)**
- **Joubert Syndrome (9 genes)**
- **Inherited Metabolic Diseases (41 genes)**
- **Epilepsy in X-linked Intellectual Disability (18 genes)**
- **Syndromic Disorders (71 genes)**
- **Brain or Nervous System Malformations (50 genes)**
- **Other (12 genes)**

Genetic Basis of Epilepsy

- A recent study by Lemke et al. using a 256-gene Next Generation Sequencing panel found a genetic cause in nearly 50% of epilepsy patients.¹ The yield varies by specific diagnosis, which might include Dravet syndrome, infantile spasms, benign familial neonatal and neonatal-infantile seizures (BFNS and BFNIS), generalized epilepsy with febrile seizures plus (GEFS+) and Lafora disease.^{2,3,4}
- Inherited epilepsies can follow any pattern: autosomal dominant, autosomal recessive, or X-linked. Specific genetic syndromes that can present with epilepsy include Walker-Warburg syndrome, Krabbe disease, and Angelman syndrome.^{5,6}
- Effective treatments and management vary by diagnosis; therefore, genetic testing can confirm or establish a diagnosis, allowing clinicians to direct management or to prevent ineffective, or even contraindicated, treatments.

Indications for Testing

- Molecular confirmation of a clinical diagnosis or suspicion of epilepsy
- To assist with treatment and management decisions
- Testing for previously identified mutation(s) in family members of an affected individual

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Description of Data Categories:

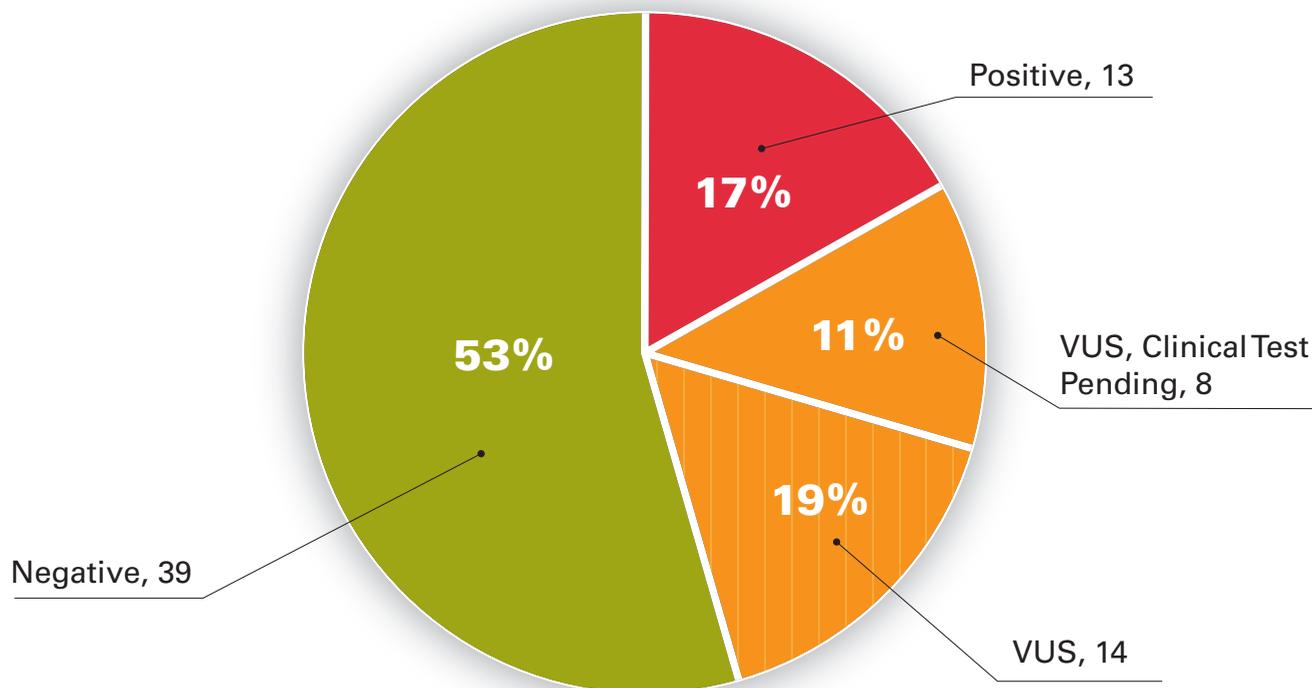
- **Positive and Likely Positive:** Variants identified are associated with or predicted to be associated with disease. The variant correlates well with the phenotype presented.
- **VUS:** Variant(s) of Uncertain Significance. For most equivocal results, clinical correlation with the described phenotypes and genetic testing in relatives is recommended to clarify the clinical impact.
- **VUS: Clinical Testing Pending:** Specific clinical tests, such as an EEG or blood thiamine levels, are recommended based on the particular genetic finding, the results of which might clarify the significance of the mutation.
- **Negative:** No mutations were found that are predicted to cause disease. In many of these patients, potential risk factors for disease association were identified, which on further study in additional cases, may be found to be associated with disease.

A variant is labeled as more likely pathogenic than benign using four criteria:

- ✓ **Low population prevalence**
- ✓ **High evolutionary conservation**
- ✓ **Protein function algorithms**
- ✓ **Clinical correlation**

All proposed disease-causing mutations are verified by Sanger sequencing.

Results of 74 epiSEEK® Genetic Tests



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TABLE 1: Known conditions were identified in patients with mutations in 11 genes.

Symbol	Name	Associated Disease : Patient Phenotype
ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Chronic fatigue, abdominal pain, large bowel disease, IBS, constipation, generalized seizures, "autistic features", anxiety/panic
CASR	calcium-sensing receptor	Seizures, ADD/ADHD, hypotonia, developmental delay, loss of milestones, anxiety/panic
CASK	calcium/calmodulin-dependent serine protein kinase (MAGUK family)	No clinical information provided
CDKL5	cyclin-dependent kinase-like 5	Intractable epilepsy and developmental delay with improvement on VNS placement and ketogenic diet
CDKL5	cyclin-dependent kinase-like 5	Seizures and developmental delay
KCNQ2	potassium voltage-gated channel, KQT-like subfamily, member 2	Seizures, ataxia, spastic diplegia, autism, developmental delay and loss of milestone with normal MRI
PCDH19	protocadherin 19	Seizures and developmental delay
SCN8A	sodium channel, voltage gated, type VIII, alpha subunit	Seizures, with breakthrough seizures on Lactimal, hypotonia, constipation, slow weight gain, brain atrophy on MRI
SCN9A	sodium channel, voltage gated, type IX, alpha subunit	Autism spectrum disorder, language and sensory integration issues, hypotonia, muscle pain, seizures, asthma, GERD, constipation, IgG deficiency and severe infections with regression and temperature instability
SLC2A1	solute carrier family 2, member 1	Generalized epilepsy, spastic quadriplegia, cerebral palsy, abnormal movements (myoclonus, spasticity) and intellectual disability
SMC1A	structural maintenance of chromosomes 1A	Hypotonia, global delay, microcephaly, repetitive mouthing behaviors, dysmorphic features with normal MRI
SMC1A	structural maintenance of chromosomes 1A	Seizures, hypotonia, developmental delay, ataxia, generalized seizures (absence, myoclonic) with normal MRI
TSC1	tuberous sclerosis 1	Generalized seizures, peripheral hypotonia, autism, developmental delay, cortical vision loss, nephrocalcinosis

Case reports:

SCN8A: A 5-year-old female presented with a severe seizure disorder. She was non-verbal, microcephalic, with central hypotonia, brisk reflexes, and increased in tone in lower and upper extremities with mild contractions of her elbow and knee joints. Additional issues included constipation and slow weight gain. epiSEEK® revealed an *SCN8A* mutation which, upon further genetic testing in the family, was determined to be de novo, and therefore the likely cause of disease. *SCN8A* mutations can cause early infantile epileptic encephalopathy (EIEE) with epilepsy, cognitive impairment, behavioral problems, abnormal tone and/or cerebellar ataxia; this gene was a good fit for the patient's presentation. (11498)

SCN9A: A 7-year-old boy presented with seizures, muscle pain, autism spectrum disorder, speech and language issues, sensory integration issues, hypotonia, asthma, GER and constipation, IgG deficiency and severe infections with regression and temperature instability. epiSEEK® revealed an *SCN9A* mutation. Mutations in the *SCN9A* gene cause a spectrum of seizure disorders and have been associated with pain disorders as well. The particular missense mutations was predicted to be deleterious on the basis of its strong evolutionary conservation, its absence from 1000Genomes, in silico predictions (computer algorithms), and its reasonable fit with the patient's presentation which included seizures and pain. (11797)

Both of these mutations would have been missed by competitors' epilepsy panels that do not include *SCN8A* or *SCN9A*. The majority of the genes included in this panel are not featured on epilepsy panels offered by other diagnostic testing laboratories.

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Courtagen's Unmatched Customer Support

Saliva: A single saliva sample can provide results in weeks not months. No blood draw required.

Insurance Assistance: Courtagen works with patients, physicians and insurance carriers to pre-approve each test. Courtagen will bill the insurance company and is willing to conduct an appeals process when needed.

Courtagen Care Financial Program: For qualified patients, the Courtagen Care Financial Program can help limit out-of-pocket expenses for genetic testing to \$100 per test.

Genetic Counselors: Available to address questions regarding Courtagen test results.

Online Portal: A physician online portal is available for ordering genetic tests, and accessing patient reports when completed.

Note: The performance characteristics of this test were validated by Courtagen Life Sciences. The U.S. Food and Drug Administration (FDA) has not approved this test. However, FDA approval is currently not required for clinical use of this test. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions. Courtagen Life Sciences is a CAP accredited laboratory and is authorized under Clinical Laboratory Improvement Amendments (CLIA) to perform high-complexity testing.

References:

1. Lemke et al. (2012) Targeted next generation sequencing as a diagnostic tool in epileptic disorders. *Epilepsia*. 53:1387-98, PubMed 22612257
2. Nicita et al. (2012) The genetics of monogenic idiopathic epilepsies and epileptic encephalopathies. *Seizure*. 21:3-11, PubMed 21917483
3. Ottman et al. (2010) Genetic testing in the epilepsies--report of the ILAE Genetics Commission. *Epilepsia*. 51:655-70, PubMed 20100225
4. Pal et al. (2010) Genetic evaluation and counseling for epilepsy. *Nat Rev Neurol*. 6:445-53, PubMed 20647993
5. Pellock. (2004) Understanding co-morbidities affecting children with epilepsy. *Neurology*. 62:S17-23, PubMed 15007160
6. Pong et al. (2011) Developments in molecular genetic diagnostics: an update for the pediatric epilepsy specialist. *Pediatr Neurol*. 44:317-27, PubMed 21481738