EpiSign

Methylation Understood

EpiSign is an assay designed to readily identify proven and reproducible *epigenetic signatures* by assessing genome-wide methylation. EpiSign has multiple applications in the clinical setting by providing an additional diagnostic tool beyond the current sequencing and copy number technology paradigm.

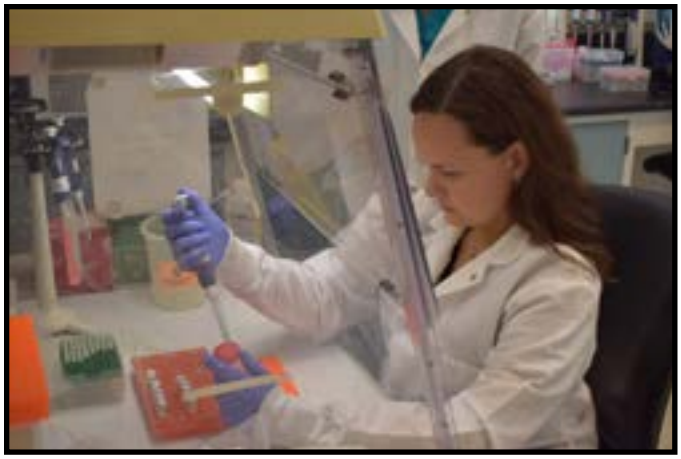
Methylation Defects

EpiSign can detect multiple methylation abnormalities associated with certain imprinting or triplet repeat conditions including Angelman syndrome, Prader-Willi syndrome, and Fragile X syndrome, among others.

Abnormalities detected using this initial screen may require additional targeted testing to confirm and further characterize the underlying genomic abnormality.

Unique Multi-locus Epigenetic Signatures

EpiSign can also identify disease-specific methylation patterns involving multiple loci across the genome. These unique methylation patterns, or epigenetic signatures, have been associated with a number of disorders. Assessment of distinct methylation patterns can be a useful screening tool for these disorders in the diagnostic work-up or can be applied in a more targeted fashion to help resolve variants of uncertain clinical significance.



EpiSign v4 features an updated algorithm including the proprietary EpiSign Meta Classifier (EMC). The EMC incorporates quantification of multiple analyses used for episignature detection enabling more standardized data analysis and interpretation, and further enhancing the accuracy of the classifier. With this approach, EpiSign v4 will offer improved sensitivity and specificity leading to a more objective interpretation of the data.

EpiSign v4 also introduces secondary signatures to supplement some of the heterogeneous disorder groups, including Kabuki, BAFopathy 1, and KBG syndromes. Patients who are positive for the more general, or primary, episignature will also be analyzed for the associated, secondary signatures. This approach will facilitate a more targeted downstream testing strategy when a genetic variant has not yet been identified.

Greenwood Diagnostic Labs
Giving Greater Care

in partnership with

London Health Sciences Centre
St Joseph's Health Care London
Pathology and Laboratory Medicine

Greenwood Diagnostic Laboratories in partnership with London Health Science Centre present *EpiSign*.

Conditions with Strong Signatures	Related Region or Gene(s)
Alpha-thalassemia X-linked Intellectual Disability	*ATRX*
BAFopathy 1: including Coffin-Siris syndromes & Nicolaides-Baraitser[1]	*ARID1A, ARID1B, SMARCB1, SMARCA4, SMARCA2*
Secondary signatures :	
Coffin-Siris syndrome 1[2]	*ARID1B*
Coffin-Siris syndrome 2[2]	*ARID1A*
Coffin-Siris syndrome 3[2]	*SMARCB1*
Coffin-Siris syndrome 4[2]	*SMARCA4*
Nicholaides-Baraitser[2]	*SMARCA2*
BAFopathy 2: Coffin-Siris syndrome 1 & 2 (c.6200)[3]	*ARID1A* (c.6133-c.6254), *ARID1B* (c.6133-c.6254)
Beck-Fahrner syndrome[4,5]	*TET3*
Blepharophimosis-impaired intellectual development syndrome	*SMARCA2*
CHARGE syndrome	*CHD7*
Coffin-Siris syndrome 4[6]	*SMARCA4* (c.2656)
Cornelia de Lange syndromes 1-4[7]	*NIPBL, RAD21, SMC3, SMC1A*
Developmental and epileptic encephalopathy 94	*CHD2*
Down syndrome	Trisomy 21
Dystonia 28, childhood-onset	*KMT2B*
Floating-Harbor syndrome	*SRCAP*
Helsmoortel-Van der Aa syndrome[8]	*ADNP*
Hunter-McAlpine craniosynostosis syndrome	5q35-qter duplication (Chr5:172,801,352_180,719,789) involving *NSD1*
Intellectual Developmental Disorder with seizures and language delay	*SETD1B*
Kabuki syndrome 1 & 2	*KDM6A, KMT2D*
Secondary signatures :	
Kabuki syndrome 1[2]	*KMT2D*
Kabuki syndrome 2[2]	*KDM6A*
KDM2B-related syndrome	*KDM2B*
Kleefstra syndrome 1	*EHMT1*
Klinefelter syndrome	47, *XXY*
Koolen-De Vries syndrome	*KANSL1*
Luscan-Lumish syndrome	*SETD2*
Menke-Hennekam syndrome 1 & 2 (IDR4 domain only)[9]	*CREBBP* (c.5563-5614), *EP300* (c.5471-5495)
Phelan-McDermid syndrome[10]	22q13.3 deletion (Chr22:45,277,036_51,244,566)
PRC2 complex disorders: Weaver & Cohen-Gibson syndromes[11]	*EZH2, EED*
Rahman syndrome	*H1-4 (HIST1H1E)*
Rubinstein-Taybi syndromes 1 & 2	*CREBBP, EP300*
Secondary signatures :	
Rubinstein-Taybi syndrome 1[2]	*CREBBP*
Rubinstein-Taybi syndrome 2[2]	*EP300*
Sifrim-Hitz-Weiss syndrome	*CHD4*

Genes/conditions listed in blue are new signatures for EpiSign v4.

The first clinical assay validated to detect unique epigenetic signatures and methylation abnormalities for clinically recognized genetic conditions.

Smith-Magenis syndrome[12]	17p11.2 deletion (Chr17:15,363,233_22,150,448)
Sotos syndrome	*NSD1*
Velocardiofacial syndrome	22q11.2 deletion (Chr22:16,888,899_21,800,797)
White-Sutton syndrome	*POGZ*
Wiedemann-Steiner syndrome	*KMT2A*
Williams-Beuren region duplication syndrome	7q11.23 duplication (Chr7:72,745,047_74,138,460)
Williams-Beuren syndrome	7q11.23 deletion (Chr7:72,744,455_74,142,510)
X-linked syndromic intellectual developmental disorder, Claes-Jensen type [4,13]	*KDM5C*
Wolf-Hirschhorn syndrome[14]	4p16.3 deletion (Chr4:34,021_24,136,683) involving *NSD2*

Conditions with Moderate Signatures	Related Region or Gene(s)
1p36 deletion syndrome	1p36 deletion (Chr1:835,601_11,565,652)
Autosomal Dominant Cerebellar Ataxia. Deafness, Narcolepsy (ADCADN)	*DNMT1*
Autosomal Dominant Intellectual Developmental Disorder Type 23, KBG syndrome[15]	*SETD5, ANKRD11*
Secondary signatures :	
Intellectual Developmental Disorder, autosomal dominant, type 23[2]	*SETD5*
KBG syndrome[2]	*ANKRD11*
Autosomal dominant intellectual developmental disorder, type 51[4]	*KMT5B*
Arboleda-Tham syndrome	*KAT6A*
Borjeson-Forssman-Lehmann syndrome	*PHF6*
Coffin-Siris syndrome 9	*SOX11*
Congenital Heart Defects, Dysmorphic Facial Features and Intellectual Developmental Disorder	*CCNK, CDK13*
Gabriele-de Vries syndrome	*YY1*
Genitopatellar syndrome[16]	*KAT6B*
Immunodeficiency-centromeric instability-facial anomalies syndrome, type 1[17]	*DNMT3B*
Immunodeficiency-centromeric instability-facial anomalies syndrome, types 2-4[17]	*CDCA7, ZBTB24, HELLS*
Intellectual Developmental Disorder with autism and macrocephaly	*CHD8*
Ohdo syndrome, SBBYSS variant (see also Genitopatellar syndrome)[16]	*KAT6B*
Potocki-Lupski syndrome	17p11.2 duplication (Chr17:16,429,920_20,473,937)
Renpenning syndrome	*PQBP1*
SLC32A1 related disorder	*SLC32A1*
Tatton-Brown-Rahman syndrome	*DNMT3A*
Wieacker-Wolff syndrome	*ZC4H2*
Witteveen-Kolk syndrome	*SIN3A*
X-linked intellectual developmental disorder, type 93[4]	*BRWD3*
X-linked intellectual developmental disorder, type 97	*ZNF711*
X-linked syndromic intellectual developmental disorder, Armfield type	*FAM50A*
X-linked syndromic intellectual developmental disorder, Nascimento type[18]	*UBE2A*
X-linked syndromic intellectual developmental disorder, Snyder-Robinson type	*SMS*

"The primary utility of EpiSign analysis is the assessment and reclassification of VUS in genes with existing signatures, and the assessment of genetically unsolved individuals with suspected hereditary conditions." - Genetics in Medicine, 2021

Imprinting Abnormalities	Related Region or Gene(s)
Angelman syndrome[19]	15q11.2 imprinting abnormality
Beckwith-Wiedemann syndrome	11p15 imprinting abnormality
Diabetes Mellitus, transient neonatal 1	*PLAGL1* imprinting abnormality
Fragile X syndrome[20]	*FMR1* methylation abnormality
Kagami-Ogata syndrome	*MEG3* imprinting abnormality
Mulchandani-Bhoj-Conlin syndrome	20q11-q13 imprinting abnormality involving *GNAS* complex locus
Prader-Willi syndrome	15q11.2 imprinting abnormality
Pseudohypoparathyroidism, Type 1A, 1B	20q13.32 imprinting abnormality involving *GNAS* complex locus
Russell-Silver syndrome 1	11p15 imprinting abnormality
Russell-Silver syndrome 2	UPD 7 imprinting abnormality
Temple syndrome	*MEG3* imprinting abnormality

One Assay. Two Options.

EpiSign is offered as two different tests to suit the needs of your patients.

EpiSign Complete is a comprehensive analysis that includes over 70 conditions. This test may be a useful screening tool for patients with developmental delay or with one or more overlapping features suggestive of one of the represented epigenetic signature conditions or imprinting disorders.

EpiSign Variant is a targeted review of the methylation data intended to resolve variants of uncertain clinical significance in genes with a known epigenetic signature. Pathogenic variants in these genes have an established unique signature. When present, this signature can be used to provide a supporting level of evidence for pathogenicity during variant classification.

EpiSign Complete : 0318U
EpiSign Variant : 81479
(Contact lab for price)

Sample Requirements : 3-5ml of blood in EDTA tube
(Sample collection kits available upon request)

Turnaround time : 4 weeks

Phone : +1 800.473.9411

Email : labgc@ggc.org

www.ggc.org/episign

106 Gregor Mendel Circle
Greenwood, SC 29646

Note

All coordinates are based on human genome build hg19.

Disclaimer

The listed genes and conditions have undergone a detailed review by Greenwood Diagnostic Labs, and EpiSign has been validated for clinical use. *Please note that some conditions/genes have been classified as having more moderate signatures based on signature strength, small cohort size, or types of mutations.* Females tested for X-linked conditions may have a moderate signature or a potentially false negative result. As with many clinical tests, uncertain results are possible. Please note that a normal result does not rule out the possibility that the patient is affected with one of these conditions. In some case, specific follow-up testing may be suggested to confirm or rule out a diagnosis.

Limitations

[1]Patients with pathogenic alterations in other BAFopathy genes may be detected, but not confirmed in our experiments.

[2]This is a secondary signature and requires the primary signature is postive to be reported.

[3]Only for variants near c.6200. No separate episignature due to small cohort size, however these samples cluster separately from other BAFopathy/Coffin-Siris 1&2 samples.

[4]Healthy carriers and those with incomplete penetrance are detectable.

[5]Patients with biallelic variants are distinguishable from those with monoallelic variants.

[6]Only for variants at c.2656. No separate episignature due to small cohort size, however these samples cluster separately from other BAFopathy/Coffin-Siris 4 samples.

[7]*HDAC8* for males may also be detected, but this finding has not been confirmed.

[8]Helsmoortal-van der Aa syndrome consists of two distinct episignatures dependent on variant location. HVDAS_T includes variants within the N- and C- terminus while HVDAS_C includes variants within the central region (approximately c.2054-2340).

[9]Only for domain IDR4. Menke-Hennekam 1&2 exhibit a shared IDR4 domain episignature and therefore cannot distinguish between Menke-Hennekam syndrome 1&2. Other domains of Menke-Hennekam 1&2 are not available for assessment.

[10]Only for copy number variants. Sequence variants in *SHANK3* have been shown not to match the episignature.

[11]Shared episignatures between PRC2 complex syndromes Weaver syndrome and Cohen-Gibson syndrome.

[12]Only for copy number variants. Sequence variants in *RAI1* have been shown not to match the episignature.

[13]Heterozygotes have a distinct profile from hemizygotes.

[14]Wolf-Hirschhorn syndrome episignatures can detect truncating variants in *NSD2.*

[15]KBG syndrome and Intellectual Disability, autosomal dominant, 23 share a common episignature. Separate episignatures will be used as secondary signatures, with sample positivity for the combined episignature required.

[16]Genitopatellar syndrome & SBBYS syndrome are both caused by *KAT6B* mutations. We will report both regardless of which one is requested.

[17]Immunodeficiency-centromeric instability facial anomalies syndrome 1 exhibits a unique episignature while syndromes 2-4 exhibit a distinct, and shared, episignature.

[18]Carriers have not been detected in our experiments.

[19]A methylation signature has not been developed for patients with sequence variants in *UBE3A*.

[20]Females with repeat expansions in *FMR1* cannot be detected with this assay.

About Greenwood Genetic Center

The Greenwood Genetic Center is a nonprofit institute organized to provide clinical genetic services, diagnostic laboratory testing, educational programs and resources and research in the field of medical genetics.