Methylation Array Panel content for EpiSign version 5

NWGLH in partnership with EpiSign, London Health Science Centre

Episignatures are reproducible DNA methylation patterns, or biomarkers, associated with a specific genetic disorder. The current EpiSign version 5 contains known episignatures for the following disorders:

New signatures on V5 of the panel compared to V4

Disorder	Gene or Region	Notes
Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant	DNMT1	Reduced sensitivity may be observed.
ARID1A duplication-related syndrome	ARID1A	The range of validated coordinates is 1p36.11(26,964,202-27,099,490). CNVs overlapping or expanding this region may also be detected. Reduced sensitivity may be observed.
Arboleda-Tham syndrome	KAT6A	Reduced sensitivity may be observed.
Alpha-thalassemia/Impaired intellectual development syndrome, X-linked	ATRX	Episignature defined with male cases only. Heterozygotes have been shown to not match the episignature.
BAFopathies: Coffin-Siris (CSS1-4) & Nicolaides-Baraitser (NCBRS) syndromes	ARID1A, ARID1B, SMARCB1, SMARCA4, SMARCA2	Patients with other BAFopathy genes may be detected.
Branchial arch abnormalities, choanal atresia, athelia, hearing loss, and hypothyroidism syndrome	KMT2D	Only for variants within the amino acid range of 3400-3700. Reduced sensitivity may be observed.
Beck-Fahrner syndrome	TET3	Healthy carriers and those with incomplete penetrance are detectable. Patients with biallelic variants are distinguishable from those with monoallelic variants.
Börjeson-Forssman-Lehmann syndrome	PHF6	This is a secondary episignature; sample must also be positive for the combined Börjeson-Forssman-Lehmann, Chung-Jansen and White Kernohan syndromes signature. Episignature defined with male cases only. Heterozygotes have been shown to not match the episignature. Reduced sensitivity may be observed.
Blepharophimosis-impaired intellectual development syndrome	SMARCA2	
Cornelia de Lange syndromes 1-4	NIPBL, RAD21, SMC3, SMC1A	
Cornelia de Lange syndrome 1	NIPBL	This is a secondary episignature; sample must also be positive for Cornelia de Lange syndromes 1-4 signature. Reduced sensitivity may be observed.
Cornelia de Lange syndrome 2	SMC1A	This is a secondary episignature; sample must also be positive for Cornelia de Lange syndromes 1-4 signature. Reduced sensitivity may be observed.
Cornelia de Lange syndrome 3	SMC3	This is a secondary episignature; sample must also be positive for Cornelia de Lange syndromes 1-4 signature. Reduced sensitivity may be observed.
Cornelia de Lange syndrome 4	RAD21	This is a secondary episignature; sample must also be positive for Cornelia de Lange syndromes 1-4 signature. Reduced sensitivity may be observed.
CHARGE syndrome	CHD7	
Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder	CDK13, CCNK	Reduced sensitivity may be observed.
Chromosome 19p13.13 deletion syndrome	Chr19p13.13p13.2 deletion	The range of validated coordinates is 19p13.13p13.2(13,201,983-13,213,144). CNVs overlapping or expanding this region may also be detected. Only for copy number variants. NFIX sequence variants have been shown to not match the episignature.
Chromosome 1p36 deletion syndrome	Chr1p36 deletion	The range of validated coordinates is 1p36.33p36.32(1,019,753-2,867,961). CNVs overlapping or expanding this region may also be detected. Reduced sensitivity may be observed.

Chromosome Xp11.22 duplication syndrome	ChrXp11.22 duplication	The range of validated coordinates is Xp11.22(53,559,057-53,654,518). CNVs overlapping or expanding this region may also be detected. Episignature defined with male cases only. Heterozygotes have been shown to not match the episignature. Reduced sensitivity may be observed.
Börjeson-Forssman-Lehmann, Chung-Jansen and White Kernohan syndromes	PHIP, PHF6, DDB1	
Chung-Jansen syndrome	PHIP	This is a secondary episignature; sample must also be positive for the combined Börjeson-Forssman-Lehmann, Chung-Jansen and White Kernohan syndromes signature. Reduced sensitivity may be observed.
Clark-Baraitser syndrome	TRIP12	
BAFopathies: Coffin-Siris syndrome 1 & 2	ARID1A, ARID1B	Only for variants near c.6200.
Coffin-Siris syndrome 1	ARID1B	This is a secondary episignature; sample must also be positive for BAFopathy. Reduced sensitivity may be observed.
Coffin-Siris syndrome 2	ARID1A	This is a secondary episignature; sample must also be positive for BAFopathy. Reduced sensitivity may be observed.
Coffin-Siris syndrome 3	SMARCB1	This is a secondary episignature; sample must also be positive for BAFopathy. Reduced sensitivity may be observed.
Coffin-Siris syndrome 4	SMARCA4	This is a secondary episignature; sample must also be positive for BAFopathy. Reduced sensitivity may be observed.
Coffin-Siris syndrome 4	SMARCA4	Only for variants near c.2656. No separate episignature due small cohort size however these samples cluster separately from other BAFopathy/CSS4 samples.
Coffin-Siris syndrome 6	ARID2	
Developmental and epileptic encephalopathy 54	HNRNPU	
Developmental and epileptic encephalopathy 94	CHD2	
DEGCAGS syndrome	ZNF699	Heterozygotes have been shown to not match the episignature.
Developmental delay with variable intellectual disability and dysmorphic facies	JARID2	Reduced sensitivity may be observed.
Diets-Jongmans syndrome	KDM3B	
Down syndrome	Chr21 trisomy	
Williams-Beuren region duplication syndrome	Chr7q11.23 duplication	The range of validated coordinates is 7q11.23(73,953,518-74,138,459). CNVs overlapping or expanding this region may also be detected.
Dystonia 28, childhood-onset	KMT2B	
Fanconi anemia	FANCA, FANCC, FANCD2, FANCG, FANCI, FANCL	Heterozygotes have been shown to not match the episignature. Patients with other FANC genes may be detected.
Floating Harbour syndrome	SRCAP	
Gabriele-de Vries syndrome	YY1	Reduced sensitivity may be observed.
Genitopatellar syndrome	KAT6B	Reduced sensitivity may be observed. Since GTPTS and SBBYSS are both caused by variants in KAT6B, it is recommended to request both episignatures for VUS assessment.
Hao-Fountain syndrome	USP7	
Hunter McAlpine craniosynostosis syndrome	Chr5q35 duplication involving NSD1	The range of validated coordinates is 5q35.2q35.3(175,839,681-176,904,798). CNVs overlapping or expanding this region may also be detected.
Helsmoortel-van der Aa syndrome	ADNP	Central episignature for variants within the coding nucleotide range of c.2054-2340.
Helsmoortel-van der Aa syndrome	ADNP	Terminal episignature for variants outside of the coding nucleotide range of c.2054-2340.

Immunodeficiency-centromeric instability-facial anomalies syndrome 1	DNMT3B	Reduced sensitivity may be observed.
Immunodeficiency-centromeric instability-facial anomalies syndrome 2-4	CDCA7, ZBTB24, HELLS	Reduced sensitivity may be observed.
Intellectual developmental disorder with autism and macrocephaly	CHD8	Reduced sensitivity may be observed.
Intellectual developmental disorder with microcephaly and with or without ocular malformations or hypogonadotropic hypogonadism	SOX11	Reduced sensitivity may be observed.
Intellectual developmental disorder with seizures and language delay	SETD1B	
Intellectual developmental disorder with dysmorphic facies, speech delay, and T-cell abnormalities	BCL11B	Reduced sensitivity may be observed.
Kabuki syndrome 1 & 2	KMT2D, KDM6A	
Kabuki syndrome 1	KMT2D	This is a secondary episignature; sample must also be positive for Kabuki. Reduced sensitivity may be observed.
Kabuki syndrome 2	KDM6A	This is a secondary episignature; sample must also be positive for Kabuki. Reduced sensitivity may be observed.
KBG syndrome	ANKRD11	This is a secondary episignature; sample must also be positive for KBGS_MRD23. Reduced sensitivity may be observed.
Intellectual developmental disorder, autosomal dominant 23; KBGS syndrome	SETD5, ANKRD11	
KDM2B-related syndrome	KDM2B	
Koolen de Vreis syndrome	KANSL1	
Kleefstra syndrome 1	EHMT1	
Luscan-Lumish syndrome	SETD2	
Menke-Hennekam syndrome 1 & 2	CREBBP, EP300	Only for domain ID4. MKHK1 and MKHK2 exhibit a shared ID4 domain episignature and therefore cannot distinguish between MKHK1 and MKHK2. Other domains of MKHK1/2 are not available.
Mowat-Wilson syndrome	ZEB2	
Intellectual developmental disorder, autosomal dominant 21	CTCF	
Intellectual developmental disorder, autosomal dominant 23	SETD5	This is a secondary episignature; sample must also be positive for KBGS_MRD23. Reduced sensitivity may be observed.
Intellectual developmental disorder, autosomal dominant 51	KMT5B	Healthy carriers and those with incomplete penetrance are detectable. Reduced sensitivity may be observed.
Intellectual developmental disorder, autosomal dominant 7	DYRK1A	
Intellectual developmental disorder, X-linked, syndromic, Armfield type	FAM50A	Episignature defined with male cases only. Heterozygotes have been shown to not match the episignature. Reduced sensitivity may be observed.
Intellectual developmental disorder, X-linked, syndromic, Claes-Jensen type	KDM5C	Healthy carriers and those with incomplete penetrance are detectable. Heterozygotes have a distinct profile from hemizygotes.
Intellectual developmental disorder, X-linked syndromic, Nascimento type	UBE2A	Episignature defined with male cases only. Heterozygotes have been shown to not match the episignature. Reduced sensitivity may be observed.
Intellectual developmental disorder, X-linked, syndromic, Snyder-Robinson type	SMS	Episignature defined with male cases only. Reduced sensitivity may be observed.

MSL2-related syndrome	MSL2	Reduced sensitivity may be observed.
Nicolaides-Baraitser syndrome	SMARCA2	This is a secondary episignature; sample must also be positive for BAFopathy. Reduced sensitivity may be observed.
Neurodevelopmental disorder with dysmorphic facies and behavioral abnormalities	SRSF1	
Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language	MEF2C	
NSD2 duplication-related syndrome	NSD2	The range of validated coordinates is 4p16.3(1,832,733-1,975,031). CNVs overlapping or expanding this region may also be detected.
Phelan-McDermid syndrome	Chr22q13.3 deletion	The range of validated coordinates is 22q13.3(49,238,268-50,248,907). CNVs overlapping or expanding this region may also be detected. Only for copy number variants. SHANK3 sequence variants have been shown to not match the episignature.
PRC2 complex disorders (Weaver and Cohen-Gibson syndromes)	EZH2, EED	Shared episignature between PRC2 complex syndromes WVS and COGIS. IMMAS (Imagawa-Matsumoto syndrome) cases with variants in SUZ12 have also been detected.
Neuroocular syndrome	PRR12	Healthy carriers and those with incomplete penetrance are detectable. Reduced sensitivity may be observed.
Pitt-Hopkins syndrome	TCF4	
Potocki-Lupski syndrome	Chr17p11.2 duplication	The range of validated coordinates is 17p11.2(16,779,412-20,231,379). CNVs overlapping or expanding this region may also be detected. Reduced sensitivity may be observed.
Renpenning syndrome	PQBP1	Episignature defined with male cases only. Heterozygotes have been shown to not match the episignature. Reduced sensitivity may be observed.
Rahman syndrome	H1-4	
Rubinstein-Taybi syndrome 1 and 2	CREBBP, EP300	
Rubinstein-Taybi syndrome 1	CREBBP	This is a secondary episignature; sample must also be positive for RSTS.
Rubinstein-Taybi syndrome 2	EP300	This is a secondary episignature; sample must also be positive for RSTS.
Ohdo syndrome, SBBYSS variant	KAT6B	Reduced sensitivity may be observed. Since GTPTS and SBBYSS are both caused by variants in KAT6B, it is recommended to request both episignatures for VUS assessment.
Sifrim-Hitz-Weiss syndrome	CHD4	
SLC32A1-related syndrome	SLC32A1	Reduced sensitivity may be observed.
Smith-Magenis syndrome	Chr17p11.2 deletion	The range of validated coordinates is 17p11.2(17,322,913-18,515,769). CNVs overlapping or expanding this region may also be detected. Only for copy number variants. RAI1 sequence variants have been shown to not match the episignature.
Sotos syndrome	NSD1	
Tatton-Brown-Rahman syndrome	DNMT3A	Reduced sensitivity may be observed.
Turner syndrome	ChrX deletion; 45,X	
Velocardiofacial syndrome	Chr22q11.2 deletion	The range of validated coordinates is 22q11.21(19,510,547-20,285,090). CNVs overlapping or expanding these regions may be detected.
Wiedemann-Steiner syndrome	KMT2A	
White-Kernohan syndrome	DDB1	This is a secondary episignature; sample must also be positive for the Börjeson-Forssman-Lehmann, Chung-Jansen and White Kernohan syndromes signature Reduced sensitivity may be observed.
Wolf-Hirschhorn syndrome & Rauch-Steindl syndrome	Chr4p16.3 deletion, NSD2	The range of validated coordinates is 4p16.3(679,715-2,169,001). CNVs overlapping or expanding this region may also be detected. NSD2 sequence variants have been shown to match the episignature.
White-Sutton syndrome	POGZ	

Williams-Beuren syndrome	Chr7q11.23 deletion	CNVs overlapping or expanding 7q11.23 may also be detected.
Witteveen-Kolk syndrome	SIN3A	Reduced sensitivity may be observed.
Wieacker-Wolff syndrome	ZC4H2	Episignature defined with male cases only. Heterozygotes have been shown to not match the episignature. Reduced sensitivity may be observed.
Intellectual developmental disorder, X-linked 93	BRWD3	Healthy carriers and those with incomplete penetrance are detectable. Reduced sensitivity may be observed.
Intellectual developmental disorder, X-linked 97	ZNF711	Heterozygotes have been shown to match the episignature. Reduced sensitivity may be observed.
Klinefelter syndrome	ChrX duplication; 47,XXY	XXX cases may also be detected.
Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase*	AHCY	Available as a single signature request only.
Diamond-Blackfan anemia 1*	RPS19	Available as a single signature request only. Reduced sensitivity against other Diamond-Blackfan anemia disorders may be observed.
Diamond-Blackfan anemia 5*	RPL35A	Available as a single signature request only. Reduced sensitivity against other Diamond-Blackfan anemia disorders may be observed.
Developmental delay with or without dysmorphic facies and autism*	TRRAP	Available as a single signature request only. Only for variants within the amino acid range of 960-1159.
Desanto-Shinawi syndrome*	WAC	Available as a single signature request only.
Hypercholesterolemia, familial, 1*	LDLR	Available as a single signature request only. Sensitivity against other hereditary hypercholesterolemia disorders has not been evaluated. Both monoallelic and biallelic cases are detected.
Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities*	FBXO11	Available as a single signature request only.
KMT2C-related syndrome*	KMT2C	Available as a single signature request only. Reduced sensitivity and specificity may be observed.
Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities*	ZMYM2	Available as a single signature request only.
PHF12-related syndrome*	PHF12	Available as a single signature request only.
SETD1A-related syndrome*	SETD1A	Available as a single signature request only.
Schuurs-Hoeijmakers syndrome*	PACS1	Available as a single signature request only. Reduced sensitivity may be observed.
Intellectual developmental disorder, X-linked 112*	ZMYM3	Available as a single signature request only. Episignature defined with male cases only. Reduced sensitivity and specificity may be observed.
Coffin-Siris syndrome 12*	BICRA	Available as a single request only. Reduced sensitivity and specificity may be observed.
TLK2-related Intellectual developmental disorder 57*	TLK2	Available as a single request only.
X-Linked PHF8-related Intellectual developmental disorder, Siderius type*	PHF8	Available as a single request only. Episignature defined with male cases only.
Neurofibromatosis, type 1*	NF1	Available as a single request only
NOTCH1-associated syndrome*	NOTCH1	Available as a single request only
Tessadori-Bicknell-van Haaften neurodevelopmental syndrome 1, 3 and 4*	H4C4, H4C4, H4C5, H4C9	Available as a single request only

*These signatures are available as a single request only. They are, at present not part of the multiclass classifier and should be requested where there is a plausible VUS in the gene, or a highly specific clinical presentation.

Epivariants are a DNA methylation pattern of a small number of CpGs at a specific region of the genome which are associated with a specific disorder. The current EpiSign version 5 will detect epivariants associated with the following imprinting and trinucleotide repeat disorders:

Disorder	Gene or Region
Fragile X syndrome (Affected males ONLY)	FMR1 promoter
Angelman syndrome	15q11.2-q13 (SNRPN promoter, SNURF)
Beckwith-Wiedemann syndrome	11p15.5 (IC1 and IC2)
Kagami-Ogata syndrome	14q32 (MEG3 promoter)
Mulchandani-Bhoj-Conlin syndrome	20q11-q13 (GNAS)
Multi-locus imprinting disturbances	All EpiSign imprinting regions
Pseudohypoparathyroidism IA & IB	20q11-q13 (GNAS)
Prader-Willi syndrome	15q11.2-q13 (SNRPN promoter, SNURF)
Silver-Russell syndrome 1 & 2	11p15.5 (IC1 and IC2), 7q32.2
Temple syndrome	14q32 (MEG3 promoter)
Diabetes mellitus, transient neonatal 1	6q24 (PLAGL1)