Appendix

Table 1. Conditions Only Available as Targeted Episignature Analysis by Request

**Reduced sensitivity and/or specificity may be observed.*

Conditions	Related regions/genes
Coffin-Siris syndrome 12*	BICRA*
Desanto-Shinawi syndrome	WAC
Developmental delay with or without dysmorphic facies and autism	TRRAP (only for variants p.960-p.1159)
Diamond-Blackfan anemia 1*	RPS19*
Diamond-Blackfan anemia 5*	RPL35A*
Fetal Valproate syndrome	Not applicable
Hypercholesterolemia, familial, 1 *Sensitivity against other hereditary hypercholesterolemia disorders has not been evaluated. Both monoallelic and biallelic cases are detected.*	LDLR
Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase	AHCY
Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities	FBXO11
Intellectual developmental disorder, autosomal dominant 57	TLK2
Intellectual developmental disorder, X-linked 112*	ZMYM3* (male cases only)
Intellectual developmental disorder, X-linked syndromic, Siderius type	PHF8 (male cases only)
KMT2C-related syndrome*	KMT2C*
Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities	ZMYM2
Neurofibromatosis, type 1*	NF1*
NOTCH1 associated syndrome*	NOTCH1*
PHF12-related syndrome	PHF12
Recurrent constellations of embryonic malformations *Includes cases with phenotypic presentation of OAV, OAVV, VACTERL and VATER.*	Not applicable
Schuurs-Hoeijmakers syndrome*	PACS1*
SETD1A-related syndrome	SETD1A
Tessadori-Bicknell-van Haaften neurodevelopmental syndrome 1, 3 and 4	H4C3, H4C4, H4C5, H4C9

Table 2. Complete Episignature Analysis I: Fragile X Syndrome and Imprinting Disorders

Conditions	Related regions/genes
Angelman syndrome (AS) *The SNRPN promoter is sensitive but not specific for AS and only reported with a positive result for SNURF.*	15q11.2-q13 (SNRPN promoter, SNURF)
Prader-Willi syndrome (PWS) *The SNRPN promoter is sensitive but not specific for PWS and only reported with a positive result for SNURF.*	15q11.2-q13 (SNRPN promoter, SNURF)
Beckwith-Wiedemann syndrome	11p15.5 (IC1 and IC2)
Silver Russel syndrome 1 & 2	11p15.5 (IC1 and IC2), 7q32.2
Diabetes mellitus, transient neonatal 1	6q24 (PLAGL1)
Fragile X syndrome	FMR1 promoter
Kagami-Ogata syndrome	14q32 (MEG3 promoter)
Mulchandani-Bhoj-Conlin syndrome	20q11-q13 (GNAS)
Multi-locus imprinting disturbances *Only positive sites will be reported.*	All EpiSign imprinting regions
Pseudohypoparathyroidism IA & IB	20q11-q13 (GNAS)
Temple syndrome	14q32 (MEG3 promoter)

Table 3. Complete Episignature Analysis II: Single Gene and Chromosomal Disorders

**Reduced sensitivity may be observed. All genomic coordinates are provided in accordance with GRCh37/hg19.*

Conditions	Related Regions/Genes
Alpha-thalassemia/Impaired intellectual development syndrome, X-linked	ATRX (male cases only)
Arboleda-Tham syndrome*	KAT6A*
ARID1A duplication-related syndrome* *CNVs overlapping or expanding this region may also be detected.*	ARID1A dup* (Chr1: 26,964,202-27,099,490)
BAFopathies: Coffin-Siris syndrome (CSS) 1-4 & Nicolaides-Baraitser syndromes	ARID1A, ARID1B, SMARCB1, SMARCA4, SMARCA2
•Coffin-Siris syndrome 1*	ARID1B*
•Coffin-Siris syndrome 2*	ARID1A*
•Coffin-Siris syndrome 3*	SMARCB1*
•Coffin-Siris syndrome 4*	SMARCA4*
•Nicolaides-Baraitser syndrome*	SMARCA2*
•*Secondary signatures must also be positive for BAFopathy. Patients with other BAFopathy genes may be detected, but not confirmed.*	
BAFopathies: Coffin-Siris syndrome 1 & 2 (only for variants near c.6200)	ARID1A, ARID1B (near c.6200 in both genes)

No separate episignature due to small cohort size, however these samples cluster separately from other BAFopathy/CSS1&2 samples.	
Coffin-Siris syndrome 6	ARID2
Beck-Fahrner syndrome *Healthy carriers and those with incomplete penetrance are detectable. Patients with biallelic variants are distinguishable from those with monoallelic variants.*	TET3
Blepharophimosis-impaired intellectual development syndrome	SMARCA2
Börjeson-Forssman-Lehmann, Chung-Jansen and White Kernohan syndromes (CHU_BFL_WHI) •Börjeson-Forssman-Lehmann syndrome* •Chung-Jansen syndrome* •White-Kernohan syndrome* *•Secondary signatures must also be positive for CHU_BFL_WHI.*	PHIP, PHF6, DDB1 PHF6* (male cases only) PHIP* DDB1*
Branchial arch abnormalities, choanal atresia, athelia, hearing loss, and hypothyroidism syndrome*	KMT2D* (only for variants within p.3400-p.3700)
Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant*	DNMT1*
CHARGE syndrome	CHD7
Chromosome 1p36 deletion syndrome* *CNVs overlapping or expanding this region may also be detected.*	1p36 del* (Chr1: 1,019,753-2,867,961)
Chromosome 19p13.13 deletion syndrome *CNVs overlapping or expanding this region may also be detected. Only for CNVs. NFIX sequence variants not match the episignature.*	19p13.13p13.2 del (Chr19: 13,201,983-13,213,144)
Chromosome Xp11.22 duplication syndrome* *CNVs overlapping or expanding this region may also be detected. Male cases only.*	Xp11.22 dup* (ChrX: 53,559,057-53,654,518)
Clark-Baraitser syndrome	TRIP12
Congenital heart defects, dysmorphic facial features, and Intellectual DD*	CDK13*, CCNK*
Cornelia de Lange syndromes (CdLs) 1-4 •Cornelia de Lange syndrome 1* •Cornelia de Lange syndrome 2* •Cornelia de Lange syndrome 3* •Cornelia de Lange syndrome 4* *Male CdLS5 patients (HDAC8 mutations) may be detected, but not confirmed. •Secondary signatures must also be positive for CdLs1-4.*	NIPBL, RAD21, SMC3, SMC1A NIPBL* SMC1A* SMC3* RAD21*
DEGCAGS syndrome *Heterozygotes have been shown to not match the episignature.*	ZNF699
Developmental and epileptic encephalopathy 54	HNRNPU
Developmental and epileptic encephalopathy 94	CHD2
Developmental delay with variable intellectual disability and dysmorphic facies*	JARID2*
Diets-Jongmans syndrome	KDM3B
Down syndrome	Trisomy 21
Dystonia 28, childhood-onset	KMT2B
Fanconi anemia *Heterozygotes have been shown to not match the episignature. Patients with other FANC genes may be detected, but not confirmed.*	FANCA, FANCC, FANCD2, FANCG, FANCI, FANCL
Floating Harbour syndrome	SRCAP
Gabriele-de Vries syndrome*	YY1*
Genitopatellar syndrome (GTPTS)* and Ohdo syndrome, SBBYSS variant* *Since GTPTS and SBBYSS are both caused by variants in KAT6B, it is recommended to request both episignatures for VUS assessment.*	KAT6B*
Hao-Fountain syndrome	USP7
Helsmoortel-van der Aa syndrome _Central episignature	ADNP (only for variants within c.2054-c.2340)
Helsmoortel-van der Aa syndrome_Terminal episignature	ADNP (outside of c.2054-c.2340)
Hunter McAlpine craniosynostosis syndrome *CNVs overlapping or expanding this region may also be detected.*	5q35 dup involving NSD1 (Chr5:175839681-176904798)
Immunodeficiency-centromeric instability-facial anomalies syndrome 1*	DNMT3B*
Immunodeficiency-centromeric instability-facial anomalies syndrome 2-4*	CDCA7*, ZBTB24*, HELLS*
Intellectual developmental disorder (IDD) with autism and macrocephaly*	CHD8*
IDD with dysmorphic facies, speech delay, and T-cell abnormalities*	BCL11B*
IDD with microcephaly and with or without ocular malformations or hypogonadotropic hypogonadism*	SOX11*
Intellectual developmental disorder with seizures and language delay	SETD1B
Intellectual developmental disorder, autosomal dominant 7	DYRK1A
Intellectual developmental disorder, autosomal dominant 21	CTCF
IDD, autosomal dominant 23; KBGS syndrome (KBGS_MRD23) •IDD, autosomal dominant 23 (MRD23)* •KBG syndrome* *•Secondary signatures must also be positive for KBGS_MRD23.*	SETD5, ANKRD11 SETD5* ANKRD11*
Intellectual developmental disorder, autosomal dominant 51* *Healthy carriers and those with incomplete penetrance are detectable.*	KMT5B*
Intellectual developmental disorder, X-linked 93* *Healthy carriers and those with incomplete penetrance are detectable.*	BRWD3*

Intellectual developmental disorder, X-linked 97*	ZNF711*
Intellectual developmental disorder, X-linked syndromic, Nascimento type*	UBE2A* (male cases only)
Intellectual developmental disorder, X-linked, syndromic, Snyder-Robinson type*	SMS*
Intellectual developmental disorder, X-linked, syndromic, Armfield type*	FAM50A* (male cases only)
Intellectual developmental disorder, X-linked, syndromic, Claes-Jensen type *Healthy carriers and those with incomplete penetrance are detectable. Heterozygotes have a distinct profile from hemizygotes.*	KDM5C
Kabuki syndrome 1 & 2 •Kabuki syndrome 1* •Kabuki syndrome 2* •*Secondary signatures must also be positive for Kabuki syndrome 1 &2.*	KMT2D, KDM6A KMT2D* KDM6A*
KDM2B-related syndrome	KDM2B
Kleefstra syndrome 1	EHMT1
Klinefelter syndrome *XXX and XYY cases may also be detected.*	ChrX duplication; 47,XXY
Koolen de Vreis syndrome	KANSL1
Luscan-Lumish syndrome	SETD2
Menke-Hennekam syndrome 1 & 2 *Only for domain ID4. MKHK1 & MKHK2 exhibit a shared ID4 domain episignature and therefore cannot be distinguished. Other domains of MKHK1/2 are not available.*	CREBBP, EP300
Mowat-Wilson syndrome	ZEB2
MSL2-related syndrome*	MSL2*
Neurodevelopmental disorder with dysmorphic facies and behavioral abnormalities	SRSF1
Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language	MEF2C
Neuroocular syndrome* *Healthy carriers and those with incomplete penetrance are detectable.*	PRR12*
NSD2 duplication-related syndrome *CNVs overlapping or expanding this region may also be detected.*	NSD2 dup (Chr4: 1,832,733-1,975,031)
Phelan-McDermid syndrome *CNVs overlapping or expanding this region may also be detected. Only for CNVs. SHANK3 sequence variants do not match the episignature.*	22q13.3 del (Chr22: 49,238,268-50,248,907)
Pitt-Hopkins syndrome	TCF4
Potocki-Lupski syndrome* *CNVs overlapping or expanding this region may also be detected.*	17p11.2 dup* (Chr17:16,779,412-20,231,379)
PRC2 complex disorders (Weaver and Cohen-Gibson syndromes) *Shared episignature between PRC2 complex syndromes WVS & COGIS. Imagawa-Matsumoto syndrome cases with variants in SUZ12 have also been detected.*	EZH2, EED
Rahman syndrome	H1-4
Renpenning syndrome*	PQBP1* (male cases only)
Rubinstein-Taybi syndrome 1 and 2 (RSTS 1&2) •Rubinstein-Taybi syndrome 1 •Rubinstein-Taybi syndrome 2 •*Secondary signatures must also be positive for RSTS 1 &2.*	CREBBP, EP300 CREBBP EP300
Sifrim-Hitz-Weiss syndrome	CHD4
SLC32A1-related syndrome*	SLC32A1*
Smith-Magenis syndrome *CNVs overlapping or expanding this region may also be detected. Only for CNVs. RAI1 sequence variants do not match the episignature.*	17p11.2 del (Chr17: 17,322,913-18,515,769)
Sotos syndrome	NSD1
Tatton-Brown-Rahman syndrome*	DNMT3A*
Turner syndrome	ChrX deletion; 45,X
Velocardiofacial syndromeEpisignature Analysis by Methylation Array Appendix Table *CNVs overlapping or expanding these regions may be detected.*	22q11.2 del (Chr22: 19,510,547-20,285,090)
White-Sutton syndrome	POGZ
Wieacker-Wolff syndrome*	ZC4H2* (male cases only)
Wiedemann-Steiner syndrome	KMT2A
Williams-Beuren region duplication syndrome *CNVs overlapping or expanding this region may also be detected.*	7q11.23 dup (Chr7: 73,953,518-74,138,459)
Williams-Beuren syndrome *CNVs overlapping or expanding 7q11.23 may also be detected.*	7q11.23 deletion
Witteveen-Kolk syndrome*	SIN3A*
Wolf-Hirschhorn syndrome & Rauch-Steindl syndrome *CNVs overlapping or expanding this region may also be detected. NSD2 sequence variants have been shown to match the episignature*.	4p16.3 del involving NSD2 (Chr4: 679,715-2,169,001)