Disorder	Causative Gene or Region (OMIM#)	New for EpiSign v4
Imprinting and Trinucleotide Repeat Disorders		
Angelman syndrome (AS)	15q11.2-q13 (SNRPN promoter, SNURF) (105830)	No
Beckwith-Wiedemann syndrome (BWS)	11p15 (ICR1, KCNQ1OT1, CDKN1C) (130650)	No
Diabetes mellitus, transient neonatal 1 (TNDM1)	6q24 (PLAG1) (601410)	No
Fragile X syndrome (FXS)	FMR1 (300624)	No
Intellectual developmental disorder, FRA12A type	DIP2B promoter (136630)	No
Kagami-Ogata syndrome	14q32 (MEG3 promoter) (608149)	No
Mulchandani-Bhoj-Conlin syndrome (MBCS)	20q11-q13 (GNAS) (617352)	No
Prader-Willi syndrome (PWS)	15q11.2 (SNRPN promoter, SNURF) (176270)	No
Pseudohypoparathyroidism, Type IA, IB (PHP1A, PHP1B)	20q13.32 (GNAS) (139320/603233)	No
Silver Russel syndrome 1 (SRS1)	11p15 (ICR1) (180860)	No
Silver Russel syndrome 2 (SRS2)	7p13-q32 (618905)	No
Temple syndrome	14q32 (MEG3 promoter) (616222)	No
Episignature Disorders		
Alpha-thalassemia/Impaired intellectual development syndrome, X-linked	*ATRX* (301040)	No
Arboleda-Tham syndrome (ARTHS)	*KAT6A* (616268)	No
BAFopathies: Coffin-Siris 1-4 (CSS1, CSS2, CSS3, CSS4) & Nicolaides-Baraitser (NCBRS) syndromes[1]	*ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCA2* (135900, 614607, 614608, 614609, 601358)	No
BAFopathies: Coffin-Siris syndrome 1 and 2 (CSS1, CSS2)[2]	*ARID1B, ARID1A* c.6200 (135900, 614607)	No
Beck-Fahrner syndrome (BEFAHRS)[3,4]	*TET3* (618798)	No
Blepharophimosis-impaired intellectual development syndrome (BIS)	*SMARCA2* (619293)	No
Börjeson-Forssman-Lehmann syndrome (BFLS)	*PHF6* (301900)	No
Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant (ADCADN)	*DNMT1* (604121)	No
CHARGE syndrome	*CHD7* (214800)	No
Chr1p36 deletion syndrome	Chr1p36 deletion (607872)	Yes
Coffin-Siris syndrome-1 (CSS1)[5]	*ARID1B* (135900)	Yes
Coffin-Siris syndrome-2 (CSS2)[5]	*ARID1A* (614607)	Yes
Coffin-Siris syndrome-3 (CSS3)[5]	*SMARCB1* (614608)	Yes
Coffin-Siris syndrome-4 (CSS4)[5]	*SMARCA4* (614609)	Yes
Coffin-Siris syndrome-4 (CSS4)[6]	*SMARCA4* c.2656 (614609)	No
Coffin-Siris syndrome-9 (CSS9)	*SOX11* (615866)	No
Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder (CHDFIDD)	*CDK13, CCNK* (617360)	Yes

Disorder	Causative Gene or Region (OMIM#)	New for EpiSign v4
Cornelia de Lange syndromes 1-4 (CDLS1, CDLS2, CDLS3, CDLS4)[7]	*NIPBL, SMC1A, SMC3, RAD21* (122470, 300590, 610759, 614701)	No
Developmental and epileptic encephalopathy 94 (DEE94)	*CHD2* (615369)	No
Down syndrome	Chr21 trisomy (190685)	No
Dystonia 28, Childhood-onset (DYT28)	*KMT2B* (617284)	No
Floating-Harbour syndrome (FLHS)	*SRCAP* (136140)	No
Gabriele-de Vries syndrome (GADEVS)	*YY1* (617557)	No
Genitopatellar syndrome (see also Ohdo syndrome) (GTPTS)[8]	*KAT6B* (606170)	No
Helsmoortel-van der Aa syndrome (HVDAS)[9]	*ADNP* (615873)	No
Hunter McAlpine craniosynostosis syndrome	Chr5q35-qter duplication including *NSD1* (601379)	No
Immunodeficiency-centromeric instability-facial anomalies syndromes 1-4 (ICF1, ICF2, ICF3, ICF4)[10]	*DNMT3B, CDCA7, ZBTB24, HELLS* (242860, 614069, 616910, 616911)	No
Intellectual developmental disorder with autism and macrocephaly (IDDAM)	*CHD8* (615032)	No
Intellectual developmental disorder with seizures and language delay (IDDSELD)	*SETD1B* (619000)	No
Intellectual developmental disorder, autosomal dominant 23 (MRD23)[11]	*SETD5* (615761)	No
Intellectual developmental disorder, autosomal dominant 51 (MRD51)[3]	*KMT5B* (617788)	No
Intellectual developmental disorder, X-linked 93 (XLID93)[3]	*BRWD3* (300659)	No
Intellectual developmental disorder, X-linked 97 (XLID97)	*ZNF711* (300803)	No
Intellectual developmental disorder, X-linked syndromic, Nascimento-type (MRXSN)[12]	*UBE2A* (300860)	No
Intellectual developmental disorder, X-linked, Snyder-Robinson type (MRXSSR)	*SMS* (309583)	No
Intellectual developmental disorder, X-linked, syndromic, Armfield type (MRXSA)	*FAM50A* (300261)	No
Intellectual developmental disorder, X-linked, syndromic, Claes-Jensen type (MRXSCJ)[3, 13]	*KDM5C* (300534)	No
Kabuki syndrome 1 (KABUK1)[14]	*KMT2D* (147920)	Yes
Kabuki syndrome 1 and 2 (KABUK1, KABUK2)	*KMT2D, KDM6A* (147920, 300867)	No
Kabuki syndrome 2 (KABUK2)[14]	*KDM6A* (300867)	Yes
KBG Syndrome (KBGS)[11]	*ANKRD11* (148050)	Yes
KDM2B-related syndrome	*KDM2B* (609078)	No
Kleefstra syndrome 1 (KLEFS1)	*EHMT1* (610253)	No
Klinefelter Syndrome	XXY	Yes
Koolen de Vreis syndrome (KDVS)	*KANSL1* (610443)	No
Luscan-Lumish syndrome (LLS)	*SETD2* (616831)	No

Disorder	Causative Gene or Region (OMIM#)	New for EpiSign v4
Menke-Hennekam syndrome 1 and 2 (MKHK1, MKHK2)[15]	*CREBBP, EP300* (618332, 618333) ID4 domains	No
Nicolaides-Baraitser syndrome (NCBRS)[5]	*SMARCA2* (601358)	Yes
Ohdo syndrome, SBBYSS variant (see also Genitopatellar syndrome) (SBBYSS)[8]	*KAT6B* (603736)	No
Phelan-McDermid syndrome (PHMDS)[16]	Chr22q13.3 deletion (606232)	No
Potocki-Lupski syndrome (PTLS)	Chr17p11.2 duplication (610883)	Yes
PRC2 Complex ((Weaver syndrome (WVS) and Cohen-Gibson syndrome (COGIS))[17]	*EED, EZH2* (617561, 277590)	No
Rahman syndrome (RMNS)	*HIST1H1E* (617537)	No
Renpenning syndrome (RENS1)	*PQBP1* (309500)	No
Rubinstein-Taybi syndrome 1 (RSTS1)[18]	*CREBBP* (180849)	No
Rubinstein-Taybi syndrome 1 and 2 (RSTS1, RSTS2)	*CREBBP, EP300* (180849, 613684)	No
Rubinstein-Taybi syndrome 2 (RSTS2)[18]	*EP300* (613684)	No
Sifrim-Hitz-Weiss syndrome (SIHIWES)	*CHD4* (617159)	Yes
SLC32A1 related disorder	*SLC32A1* (616440)	Yes
Smith-Magenis syndrome (SMS)[19]	Chr17p11.2 deletion (182290)	Yes
Sotos syndrome (SOTOS)	*NSD1* (117550)	No
Tatton-Brown-Rahman syndrome (TBRS)	*DNMT3A* (615879)	No
Velocardiofacial syndrome (VCFS)	Chr22q11.2 deletion (192430)	No
White-Sutton syndrome (WHSUS)	*POGZ* (616364)	Yes
Wieacker-Wolff Syndrome (WRWF)[20]	*ZC4H2* (314580)	Yes
Wiedemann-Steiner syndrome (WDSTS)	*KMT2A* (605130)	No
Williams-Beuren region duplication syndrome	Chr7q11.23 duplication (609757)	No
Williams-Beuren syndrome (WBS)	Chr7q11.23 deletion (194050)	No
Witteveen-Kolk syndrome (WITKOS)	*SIN3A* (613406)	Yes
Wolf-Hirschhorn syndrome (WHS)[21]	Chr4p16.13 deletion, *NSD2* (194190)	No

1. Patients with other BAFopathy genes may be detected, but not confirmed in our experiments.
2. Only for variants near c.6200. No separate episignature due small cohort size, however these samples cluster separately from other BAFopathy/CSS1&2 samples.
3. Healthy carriers and those with incomplete penetrance are detectable.
4. Patients with biallelic variants are distinguishable from those with monoallelic variants.
5. This is a secondary signature; sample must also be positive for BAFopathy signature.
6. Only for variants at c.2656. No separate episignature due small cohort size however these samples cluster separately from other BAFopathy/CSS4 samples.
7. Male CdLS5 patients (HDAC8 mutations) may be detected, but not confirmed in our experiments.
8. GTPTS and SBBYSS are both caused by KAT6B mutations. We will report both regardless of which one is requested.

9. ADNP 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).
10. ICF1 exhibits a unique episignature while ICF 2, 3 and 4 exhibit a distinct, shared episignature.
11. KBGS and MRD23 share a common episignature. Separate KGBS and MRD23 episignatures will be used as secondary signatures, with sample positivity for the combined KBGS/MRD23 episignature required.
12. Carriers have not been detected in our experiments.
13. Heterozygotes have a distinct profile from hemizygotes.
14. This is a secondary signature; sample must also be positive for combined Kabuki signature.
15. Only for domain ID4. MKHK1/2 exhibit a shared ID4 domain episignature and therefore cannot distinguish between MKHK1 and MKHK2. Other domains of MKHK1/2 are not available for assessment.
16. Only for copy number variants. Sequence variants in *SHANK3* have been shown to not match the episignature.
17. Shared episignatures between PRC2 complex syndromes WVS and COGIS.
18. This is a secondary signature; sample must also be positive for combined RSTS signature.
19. Only for copy number variants. Sequence variants in *RAI1* have been shown to not match the episignature.
20. Reduced sensitivity may be observed. Defined based on affected male cases only.
21. WHS episignature can detect truncating variants in *NSD2.*

The following list of genes have been classified as having reduced sensitivity and more moderate episignatures based on episignature strength, limited reference cohort size, or types of mutations that have been tested: *ANKRD11, BRWD3, CCNK, CDCA7, CDK13, CHD8, DNMT1, DNMT3A, DNMT3B, FAM50A, HELLS, KAT6A, KAT6B, KMT5B, PHF6, PQBP1, SETD5, SIN3A, SLC32A1, SOX11, SMS, UBE2A, YY1, ZBTB24, ZC4H2, ZNF711*, Chr1p36del, Chr17p11.2dup.