# Methylation Array Panel content for EpiSign version 6.1 (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 6.1 contains known episignatures for the following disorders:

New signatures on V6.1 of the panel compared to V5.

| Episignatures | Confirmed underlying genes/regions | Notes |
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| DNMT1-related Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant | DNMT1 | Reduced sensitivity may be observed. |
| AHCY-related Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase | AHCY | Reduced sensitivity may be observed. |
| ARID1A duplication-related syndrome | ARID1A | Gene level duplication variants only |
| Arboleda-Tham syndrome | KAT6A | |
| Alpha-thalassemia/Impaired intellectual development syndrome, X-linked | ATRX | |
| BAFopathies: Coffin-Siris (CSS1-4) & Nicolaides-Baraitser (NCBRS) syndromes | ARID1A; ARID1B; DPF2; SMARCA2; SMARCA4; SMARCB1; SMARCE1 | Combined profile with ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCE1, DPF2 and SMARCA2 variants |
| KMT2D-related Branchial arch abnormalities, choanal atresia, athelia, hearing loss, and hypothyroidism syndrome | KMT2D | Defined with missense variants in exons 38-39. Reduced sensitivity may be observed. |
| Beck-Fahrner syndrome (AR and AD) | TET3 | Healthy carriers and those with incomplete penetrance are detectable. |
| Börjeson-Forssman-Lehmann syndrome | PHF6 | |
| SMARCA2-related Blepharophimosis-impaired intellectual development syndrome | SMARCA2 | Defined with missense variants outside the helicase domains. |
| Cdk13_CycK-related congenital heart defects, dysmorphic facial features, and intellectual developmental disorder | CCNK; CDK13 | Combined profile with CDK13 and CCNK variants |
| CDK13-related syndrome | CDK13 | Defined with truncating variants only. Reduced specificity may be observed. |
| Cornelia de Lange syndromes 1-4 | MAU2; NIPBL; RAD21; SMC1A; SMC3 | Combined profile with NIPBL, SMC1A, SMC3, RAD21, MAU2 and Chr5p13.2del variants. |
| NIPBL-related Cornelia de Lange syndrome 1 | NIPBL | Reduced sensitivity and specificity may be observed. |
| SMC1A-related Cornelia de Lange syndrome 2 | SMC1A | Reduced sensitivity and specificity may be observed. |

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| SMC3-related Cornelia de Lange syndrome 3 | SMC3 | Reduced sensitivity and specificity may be observed. |
| RAD21-related Cornelia de Lange syndrome 4 | RAD21 | Reduced sensitivity and specificity may be observed. |
| MAU2-related Cornelia de Lange syndrome 7 | MAU2 | |
| CHD7 disorder | CHD7 | Reduced sensitivity may be observed. |
| CHD6-related syndrome | CHD6 | |
| Chromosome 19p13.13 deletion syndrome | Chr19p13.13del | CNVs overlapping or expanding the validated 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, distal | Chr1p36del_distal | CNVs overlapping or expanding the validated region may also be detected. |
| Chromosome 8p invdupdel syndrome | Chr8 inv dup del | |
| Chromosome Xp11.22 duplication syndrome | ChrXp11.22dup | CNVs overlapping or expanding the validated region may also be detected. Reduced sensitivity may be observed. |
| Börjeson-Forssman-Lehmann, Chung-Jansen and White Kernohan syndromes | DDB1; PHF6; PHIP | Combined profile with DDB1, PHF6 and PHIP variants. |
| Chung-Jansen syndrome | PHIP | |
| Clark-Baraitser syndrome | TRIP12 | Reduced sensitivity may be observed. |
| Cohen-Gibson syndrome | Chr11q14.1q14.3del; EED | Reduced sensitivity and specificity may be observed. |
| BAFopathies: Coffin-Siris syndrome 1 & 2 | ARID1A; ARID1B | Defined with variants near c.6200 in ARID1B and ARID1A. Reduced specificity may be observed. |
| ARID1B-related Coffin-Siris syndrome 1 | ARID1B | Reduced sensitivity and specificity may be observed. |
| BICRA-related Coffin-Siris syndrome 12 | BICRA | Reduced sensitivity may be observed. |
| ARID1A-related Coffin-Siris syndrome 2 | ARID1A | Reduced sensitivity and specificity may be observed. |
| SMARCB1-related Coffin-Siris syndrome 3 | SMARCB1 | Reduced sensitivity and specificity may be observed. |
| SMARCA4-related Coffin-Siris syndrome 4 | SMARCA4 | Reduced sensitivity and specificity may be observed. |
| SMARCA4-related Coffin-Siris syndrome 5 | SMARCE1 | Reduced sensitivity and specificity may be observed. |
| ARID2-related Coffin-Siris syndrome 6 | ARID2 | |
| DFP2-related Coffin-Siris syndrome 7 | DPF2 | Reduced sensitivity and specificity may be observed. |
| Diamond-Blackfan anemias 1, 3, 4, 5, 6, 7, 8, 9, 10 | RPL11; RPL35A; RPL5; RPS17; RPS19; RPS26; RPS25; RPS7, RPS10 | DBA cases with variants in other genes may also be detected. Shwachman-Diamond cases have been shown to match the profile. |

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| TRRAP-related Developmental delay with or without dysmorphic facies and autism | TRRAP | Defined with variants within the range of p.960-1159. Reduced sensitivity may be observed. |
| HNRNPU-related Developmental and epileptic encephalopathy 54 | HNRNPU | |
| CHD2-related Developmental and epileptic encephalopathy 94 | CHD2 | |
| DEGCAGS syndrome | ZNF699 | |
| SRCAP-related disorder | SRCAP | Defined with truncating variants proximal or distal to exons 33-34. |
| Desanto-Shinawi syndrome | Chr10p12.1del; WAC | |
| U2AF2-related disorder | U2AF2 | |
| ReNU syndrome & U2AF2-related disorders | RNU4-2; U2AF2 | Combined profile with U2AF2 and RNU4-2 variants. |
| JARID2-related developmental delay with variable intellectual disability and dysmorphic facies | JARID2 | Reduced sensitivity may be observed. |
| Diets-Jongmans syndrome | KDM3B | |
| DMAP1-related syndrome | DMAP1 | Reduced sensitivity may be observed. |
| Down syndrome | Chr21 trisomy | |
| Williams-Beuren region duplication syndrome | Chr7q11.23dup | CNVs overlapping or expanding the validated region may also be detected. |
| EHMT1 duplication-related syndrome | Chr9q34.3dup | Reduced sensitivity may be observed. This episignature detects duplications involving EHMT1. CNVs overlapping or expanding EHMT1 may also be detected. |
| EHMT2-related syndrome | EHMT2 | |
| Fanconi anemia | FANCA; FANCC; FANCD2; FANCG; FANCI; FANCL | Combined profile with FANCA, FANCC, FANCD2, FANCG, FANCI and FANCL variants. FA cases with variants in other genes may also be detected. |
| Floating Harbour syndrome | SRCAP | Defined with truncating variants in exons 33-34. |
| Facioscapulohumeral muscular dystrophy 2 | SMCHD1 | Reduced sensitivity may be observed. |
| Gabriele-de Vries syndrome | YY1 | Reduced sensitivity may be observed. |
| KAT6B-related Genitopatellar syndrome | KAT6B | |
| DeSanto-Shinawi syndrome & UBE2A-related intellectual developmental disorder | UBE2A; WAC | Combined profile with Chr10p12.1del, UBE2A and WAC variants |
| Hao-Fountain syndrome | USP7 | |
| Hunter-McAlpine craniosynostosis syndrome | Chr5q35.2q35.3dup | CNVs overlapping or expanding the validated region may also be detected. |
| Helsmoortel-van der Aa syndrome | ADNP | Defined with variants located within the central gene region (c.2054-2340). |

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| DNMT3B-related Immunodeficiency-centromeric instability-facial anomalies syndrome 1 | DNMT3B | |
| CDCA7, ZBTB24 or HELLS related Immunodeficiency-centromeric instability-facial anomalies syndrome 2-4 | CDCA7; HELLS; ZBTB24 | Combined profile with ZBTB24, CDCA7 and HELLS variants. |
| CHD8-related Intellectual developmental disorder with autism and macrocephaly | CHD8; Chr14q11.2del | Reduced sensitivity may be observed. |
| FBXO11-related Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities | FBXO11 | Reduced sensitivity may be observed. |
| SOX11-related Intellectual developmental disorder with microcephaly and with or without ocular malformations or hypogonadotropic hypogonadism | SOX11 | Reduced sensitivity may be observed. |
| SETD1B-related Intellectual developmental disorder with seizures and language delay | SETD1B | |
| BCL11B-related Intellectual developmental disorder with dysmorphic facies, speech delay, and T-cell abnormalities | BCL11B | Reduced sensitivity may be observed. |
| STAT1-related Immunodeficiency 31C, chronic mucocutaneous candidiasis | STAT1 | |
| Imagawa-Matsumoto syndrome | SUZ12 | |
| Kabuki syndrome 1 | KMT2D | Reduced sensitivity and specificity may be observed. |
| Kabuki syndrome 2 | KDM6A | Reduced sensitivity and specificity may be observed. |
| KBG syndrome | ANKRD11 | |
| MSL2-related Karayol-Borroto-Haghshenas neurodevelopmental syndrome | MSL2 | Reduced sensitivity may be observed. |
| KDM5B-related neurodevelopmental disorder; Intellectual developmental disorder, autosomal dominant | KDM5B | Defined with cases with dominant inheritance (heterozygous) only. |
| KDM5B-related neurodevelopmental disorder; Intellectual developmental disorder, autosomal recessive 65 | KDM5B | Both recessive and dominant forms are detected. |
| Koolen de Vreis syndrome | KANSL1 | CNVs overlapping or expanding the validated region may also be detected. |
| Kleefstra syndrome 1 | EHMT1 | |
| KMT2B-related Dystonia 28, childhood-onset | KMT2B | Cannot distinguish DYT28 from MRD68 cases. |
| Temple syndrome | | |
| Luscan-Lumish syndrome | SETD2 | |

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| MACROH2A1-related syndrome | MACROH2A1 | Reduced sensitivity may be observed. |
| Menke-Hennekam syndrome 1 & 2 | CREBBP; EP300 | Defined with missense variants within the ID4 region. |
| MORC2-related syndrome | MORC2 | |
| Mowat-Wilson syndrome | ZEB2 | |
| CTCF-related Intellectual developmental disorder, autosomal dominant 21 | CTCF | |
| SETD5-related Intellectual developmental disorder, autosomal dominant 23 | SETD5 | |
| SETBP1-related Intellectual developmental disorder, autosomal dominant 29 | SETBP1 | Defined with truncating variants only. Reduced sensitivity may be observed. |
| KMT5B-related Intellectual developmental disorder, autosomal dominant 51 | KMT5B | Reduced sensitivity may be observed. |
| TLK2-related Intellectual developmental disorder, autosomal dominant 57 | TLK2 | |
| SET-related Intellectual developmental disorder, autosomal dominant 58 | SET | Reduced sensitivity may be observed. |
| DYRK1A-related Intellectual developmental disorder, autosomal dominant 7 | DYRK1A | |
| FAM50A-related Intellectual developmental disorder, X-linked, syndromic, Armfield type | FAM50A | Reduced sensitivity may be observed. Defined with male cases only. |
| KDM5C-related Intellectual developmental disorder, X-linked, syndromic, Claes-Jensen type (Affected males and female carriers) | KDM5C | Profile to distinguish males from females. |
| MECP2-related Intellectual developmental disorder, X-linked syndromic, Lubs type | ChrXq28dup; MECP2 | Defined with MECP2 gene level duplication variants. |
| UBE2A-related Intellectual developmental disorder, X-linked syndromic, Nascimento type | UBE2A | Reduced sensitivity may be observed. Defined with male cases only. |
| PHF8-related Intellectual developmental disorder, X-linked syndromic, Siderius type | PHF8 | Defined with male cases only. |
| SMS-related Intellectual developmental disorder, X-linked, syndromic, Snyder-Robinson type | SMS | Reduced sensitivity may be observed. Defined with male cases only. |
| Myhre syndrome | SMAD4 | |
| Nicolaides-Baraitser syndrome | SMARCA2 | Defined with missense variants within the helicase domains. Reduced sensitivity and specificity may be observed. |

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| ZMYM2-related Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities | ZMYM2 | |
| CUL3-related Neurodevelopmental disorder with or without autism or seizures | CUL3 | Reduced sensitivity may be observed. |
| KDM2B-related syndrome | KDM2B | |
| SRSF1-related Neurodevelopmental disorder with dysmorphic facies and behavioral abnormalities | SRSF1 | Reduced sensitivity may be observed. |
| MEF2C-related Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language | MEF2C | |
| DOHH-related Neurodevelopmental disorder with microcephaly, cerebral atrophy, and visual impairment | DOHH | Reduced sensitivity may be observed. |
| PRR12-related Neuroocular syndrome | PRR12 | Healthy carriers and those with incomplete penetrance are detectable. Reduced sensitivity may be observed. |
| NOTCH1-related syndrome | NOTCH1 | Reduced sensitivity may be observed. |
| NSD2 duplication-related syndrome | Chr4p16.3dup | CNVs overlapping or expanding the validated region may also be detected. |
| PHF12-related syndrome | PHF12 | Reduced sensitivity may be observed. |
| Phelan-McDermid syndrome | Chr22q13.3del | CNVs overlapping or expanding the validated 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) | EED; EZH2; SUZ12 | Combined profile with EED, EZH2, SUZ12, Chr7q36.1del, Chr11q14.1q14.3del and Chr17q11.2del variants |
| Pitt-Hopkins syndrome | TCF12; TCF4 | Combined profile with TCF4, TCF12, Chr18q21.2q21.32del and Chr15q21.2q21.3del variants |
| Potocki-Lupski syndrome | Chr17p11.2dup | CNVs overlapping or expanding the validated region may also be detected. Reduced sensitivity may be observed. |
| Rauch-Steindl syndrome | NSD2 | |
| Renpenning syndrome | PQBP1 | Reduced sensitivity may be observed. Defined with male cases only. |
| ReNU syndrome | RNU4-2 | |
| Rahman syndrome | H1-4 | |
| Rubinstein-Taybi syndrome 1 | CREBBP | Reduced sensitivity and specificity may be observed. |

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| Rubinstein-Taybi syndrome 2 | EP300 | Reduced sensitivity and specificity may be observed. |
| Ohdo syndrome, SBBYSS variant | KAT6B | |
| SETD1A-related syndrome | SETD1A | |
| Schinzel-Giedion midface retraction syndrome | SETBP1 | Defined with missense variants impacting amino acids 868-871. Reduced sensitivity may be observed. |
| Schuurs-Hoeijmakers syndrome | PACS1 | |
| Sifrim-Hitz-Weiss syndrome | CHD4 | Defined with missense variants. |
| CHD4-related syndrome | CHD4 | Defined with truncating variants. |
| Smith-Kingsmore syndrome | MTOR | Reduced sensitivity may be observed. |
| SMARCA5-related syndrome | SMARCA5 | |
| SMARCA5-related syndrome & BPTF-related neurodevelopmental disorder with dysmorphic facies and distal limb anomalies | BPTF; SMARCA5 | Combined profile with BPTF and SMARCA5 variants. |
| Smith-Magenis syndrome | Chr17p11.2del | CNVs overlapping or expanding the validated region may also be detected. Only for copy number variants. RAI1 sequence variants have been shown to not match the episignature. |
| Sotos syndrome | NSD1 | |
| Developmental delay, hypotonia, musculoskeletal defects, and behavioral abnormalities & Floating-Harbor syndrome | SRCAP | Combined profile with FLHS and DEHMBA presentations. |
| STAD syndrome | PTBP1 | |
| Tatton-Brown-Rahman syndrome | DNMT3A | |
| Tessadori-Bicknell-van Haaften neurodevelopmental syndrome 1-4, H4C4-related syndrome & H4C6-related syndrome | H4C11; H4C3; H4C4; H4C5; H4C6; H4C9 | Combined profile with H4C3, H4C11, H4C5, H4C9, H4C4 and H4C6 variants. Reduced sensitivity and specificity may be observed. |
| Turner syndrome | 45,X | |
| Velocardiofacial syndrome | Chr22q11.2del | CNVs overlapping or expanding the validated regions may be detected. |
| WAPL-related syndrome | WAPL | Reduced sensitivity may be observed. |
| PDS5B-related syndrome & WAPL-related syndrome | PDS5B; WAPL | Combined profile with PDS5B, WAPL and Chr10q22.3q23.2del truncating variants. Reduced sensitivity may be observed. |
| Williams-Beuren syndrome | Chr7q11.23del | CNVs overlapping or expanding 7q11.23 may also be detected. |
| Wiedemann-Steiner syndrome | KMT2A | |
| White-Kernohan syndrome | DDB1 | Reduced sensitivity may be observed. Reduced sensitivity and specificity may be observed. |

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| Wolf-Hirschhorn syndrome | Chr4p16.3del | CNVs overlapping or expanding the validated region may also be detected. |
| Wolf-Hirschhorn syndrome & Rauch-Steindl syndrome | Chr4p16.3del; NSD2 | Combined profile with NSD2 and Chr4p16.3del variants. |
| White-Sutton syndrome & CHAMP1-related neurodevelopmental disorder | CHAMP1; POGZ | Combined profile with CHAMP1 and POGZ variants. |
| Witteveen-Kolk syndrome | SIN3A | |
| Wieacker-Wolff syndrome | ZC4H2 | Reduced sensitivity may be observed. Defined with male cases only. |
| Weaver syndrome | EZH2 | Reduced sensitivity and specificity may be observed. |
| AHDC1 deletion-related Xia-Gibbs syndrome | AHDC1 | |
| ZMYM3-related Intellectual developmental disorder, X-linked 112 | ZMYM3 | Defined with male cases only. |
| BRWD3-related Intellectual developmental disorder, X-linked 93 | BRWD3 | Reduced sensitivity may be observed. Healthy carriers and those with incomplete penetrance are detectable. |
| ZNF711-related Intellectual developmental disorder, X-linked 97 | ZNF711 | Defined with male cases only. |
| Trisomy X | 47,XXX | |
| Klinefelter syndrome | 47,XXY | |
| Jacobs syndrome | 47,XYY | |

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 6.1 will detect epivariants associated with the following imprinting and trinucleotide repeat disorders:

| **Epivariant** | **Confirmed underlying genes/regions** | **Notes** |
|---|---|---|
| Angelman syndrome | 15q11.2-q13 (SNRPN promoter, SNURF) | |
| Beckwith-Wiedemann syndrome | 11p15 (IC1 and IC2) | |
| Diabetes mellitus, transient neonatal 1 | 6q24 (PLAG1) | |
| Fragile X syndrome | FMR1 promoter | |
| Kagami-Ogata syndrome | 14q32 (MEG3 promoter) | |
| Mulchandani-Bhoj-Conlin syndrome | 20q11-q13 (GNAS) | |
| Multi-locus imprinting disturbances | All imprinting regions on panel | |
| Prader-Willi syndrome | 15q11.2 (SNRPN promoter, SNURF) | |
| Pseudohypoparathyroidism, Type Ia, Ib | 20q13.32 (GNAS) | |
| Silver-Russel syndrome 1 | 11p15 (IC1 and IC2) | |
| Silver-Russel syndrome 2 | 7p13-q32 | |
| Temple syndrome | 14q32 (MEG3 promoter) | |
| UPD16 | ZNF597:3′ DMR | |