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|  | **Genomic Medicine Service**  **Rare Disease DNA Methylation Array Request**  (DOC5741 revision 4) | **Lab use only**  **Lab No:** Type Lab No. or Affix label |

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| **Patient Details** | | | | **Referring Clinician/Healthcare Professional** | |
| **NHS No\*:** | Enter NHS No | **D.O.B.\*:** | DD/MM/YYYY | **Consultant\*:**  (in full) | Consultant |
| **Surname\*:** | Enter Surname | **Forename\*:** | Enter Forename | **E-mail/Tel\*:** | Enter E-mail/Tel. |
| **Patient’s Address:** | Address Line 1  Address Line 2  Address Line 3 | **Biological Sex\*:** | Enter Biological sex | **Hospital/Surgery\*:**  (in full) | Enter Hospital/Surgery |
| **Ethnicity:** | Enter Ethnicity | **Department\*:** | Enter Department |
| **Postcode\*:** | Postcode | **Hospital No:** | Enter Hospital No | **Requested by/ Cc. Report to:** | Enter Requested by/Cc. Report to |

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| **Test Details\*** | **Specimen Details (EDTA Blood (1-4ml) or DNA from peripheral blood)** | |
| -Current list of genes and disorders detected by this array provided on page 3.  -By requesting this test you are confirming that this patient meets the eligibility criteria as defined by the NWGLH. Click [here](https://mft.nhs.uk/nwglh/test-information/rare-disease/) for more information regarding this service.  ***-DMNT1*** is not automatically included in the analysis due to the risk of incidental findings. If *DMNT1* is clinically relevant in this case please tick the box to include.  **DNA Methylation Array**  **Include *DMNT1* in analysis** | **High Infection risk?** Yes No | |
| **Sample Type\*:**  Blood  DNA extracted from blood | |
| **Sample Date\*:** Select Date from Calendar | |
| **Taken By:** Enter Full Name | **Sample Ref:** Reference no |
| **Further Details:** Enter any relevant details | |
| **Consent Statement:** Receipt of this form and sample(s) by the laboratory assumes that the clinician has obtained consent for genomic testing and for the use of the DNA sample(s) and/or test result(s) by healthcare professionals in the UK for family testing and quality control purposes. | | |
| **Details of variants of interest.** Please include a copy of the original genomic report, including ACGS/ACMG classification criteria. | | |
| **Clinically suspected diagnosis.** Please provide OMIM disease ID. | | |
| **Clinical Details.** Clinical information can inform the interpretation of the test. Images and additional information may be sent to mft.epipro.nwglh-lab@nhs.net. | | |
| Free text for clinical details | | |
| **Once taken, samples should be sent to the Manchester Genomics Laboratory** | | |
| [**https://mft.nhs.uk/nwglh/**](https://mft.nhs.uk/nwglh/)  **Laboratory Opening Hours: 09:00 – 17:00, Monday to Friday**  **Questions or additional information**: [mft.epipro.nwglh-lab@nhs.net](mailto:mft.epipro.nwglh-lab@nhs.net) | North West Genomic Laboratory Hub – Manchester Site  Manchester Centre for Genomic Medicine  Sample Reception (6th Floor), St Mary’s Hospital  Oxford Road, Manchester  M13 9WL  Tel: 0161 276 6122 Email: mft.genomics@nhs.net | |
| **Fields marked \* are mandatory** | | |

**For lab use only; disease code 276 DNA methylation array service**

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| **Guidance Notes – Genomic Testing Request Form – DNA Methylation Array Service** | | |
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| **Patient Details** |  | **Specimen Details** |
| The following details are mandatory, other details should be completed as fully as possible:   * **Surname** & **Forename** * **D.O.B** – Date of Birth * **NHS Number** (10 digits) * Patient’s **Biological Sex** * Patient’s **Postcode**   Please ensure a minimum of 3 matching identifiers on tubes and form.  If sending this form or additional clinical information via email please remember only to use secure nhs.net to nhs.net addresses. | **Sample Requirements:** Samples must be peripheral blood in EDTA or DNA extracted from peripheral blood. Samples in LiHep cannot be accepted.   * **For peripheral blood in EDTA** 1-4mls is required. * **For DNA from peripheral blood** a minimum amount of 1µg of DNA at 25ng/µl is required. No additional quality checks will be performed on DNA samples. It is the responsibility of the referring party to ensure DNA quality is sufficient for microarray.   **Sample Packaging:** The sample container should be sealed in a biohazard bag in case of a leakage. To prevent contamination of referral form and paperwork this should not be sealed with the sample. All packaging should conform to UN650 standards (as applied to UN3373 – Biological Samples, Category B).  **High Infection Risk:** In accordance with the Health & Safety at Work Act and COSHH Regulations, the laboratory must be informed of any infection risk associated with submitted samples. The sender has the responsibility for minimising the risk to laboratory staff by giving sufficient information to enable the laboratory to take appropriate safety precautions when testing a specimen.  **Factors known to affect the performance of the examination/interpretation of the results**: If this patient has had a bone marrow transplant/blood transfusion please contact the laboratory to discuss testing options prior to sending a sample. |
| **Referring Clinician/Healthcare Professional** |
| The following details are mandatory:   * **Consultant/GP name**: initials are not acceptable as the laboratory cannot identify the clinician/healthcare professional. A minimum of first initials and surname must be provided. * **Hospital** should be clearly identifiable; initials are not acceptable as the laboratory cannot identify the hospital. Trusts with more than one hospital should clearly identify the referring hospital. * **Department** should be clearly identifiable; initials are not acceptable as the laboratory cannot identify the department.   Other details should be completed as fully as possible:   * **E-mail/Tel**; without an email/telephone number, urgent results cannot be given. Reports will be issued via nhs.net email. Where this is not possible reports will be issued via first class post   **Requested by/Cc. Report to:** Use this space if the healthcare professional requesting the test/requiring a report copy is not the patient’s Consultant. |
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| **This area is for Lab use only** | | |  |  |

Disorders detected by EpiSign Version 4

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| **Disorder** | **Gene or Region (OMIM#)** |
| Angelman syndrome (AS) | 15q11.2-q13 (SNRPN promoter, SNURF) (105830) |
| Beckwith-Wiedemann syndrome (BWS) | 11p15 (ICR1, KCNQ1OT1, CDKN1C) (130650) |
| Diabetes mellitus, transient neonatal 1 (TNDM1) | 6q24 (PLAG1) (601410) |
| Fragile X syndrome (FXS) | FMR1 (300624) |
| Intellectual developmental disorder, FRA12A type | DIP2B promoter (136630) |
| Kagami-Ogata syndrome | 14q32 (MEG3 promoter) (608149) |
| Mulchandani-Bhoj-Conlin syndrome (MBCS) | 20q11-q13 (GNAS) (617352) |
| Prader-Willi syndrome (PWS) | 15q11.2 (SNRPN promoter, SNURF) (176270) |
| Pseudohypoparathyroidism, Type IA, IB (PHP1A, PHP1B) | 20q13.32 (GNAS) (139320/603233) |
| Silver Russell syndrome 1 (SRS1) | 11p15 (ICR1) (180860) |
| Silver Russell syndrome 2 (SRS2) | 7p13-q32 (618905) |
| Temple syndrome | 14q32 (MEG3 promoter) (616222) |
| Alpha-thalassemia/Impaired intellectual development syndrome, X-linked | ATRX (301040) |
| Arboleda-Tham syndrome (ARTHS) | KAT6A (616268) |
| BAFopathies: Coffin-Siris 1-4 (CSS1, CSS2, CSS3, CSS4) & Nicolaides-Baraitser (NCBRS) syndromes1 | ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCA2 (135900, 614607, 614608, 614609, 601358) |
| BAFopathies: Coffin-Siris syndrome 1 and 2 (CSS1, CSS2)2 | ARID1B, ARID1A c.6200 (135900, 614607) |
| Beck-Fahrner syndrome (BEFAHRS)3,4 | TET3 (618798) |
| Blepharophimosis-impaired intellectual development syndrome (BIS) | SMARCA2 (619293) |
| Börjeson-Forssman-Lehmann syndrome (BFLS) | PHF6 (301900) |
| Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant (ADCADN) | DNMT1 (604121) |
| CHARGE syndrome | CHD7 (214800) |
| Chr1p36 deletion syndrome | Chr1p36 deletion (607872) |
| Coffin-Siris syndrome-1 (CSS1)5 | ARID1B (135900) |
| Coffin-Siris syndrome-2 (CSS2)5 | ARID1A (614607) |
| Coffin-Siris syndrome-3 (CSS3)5 | SMARCB1 (614608) |
| Coffin-Siris syndrome-4 (CSS4)5 | SMARCA4 (614609) |
| Coffin-Siris syndrome-4 (CSS4)6 | SMARCA4 c.2656 (614609) |
| Coffin-Siris syndrome-9 (CSS9) | SOX11 (615866) |
| Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder (CHDFIDD) | CDK13, CCNK (617360) |
| Cornelia de Lange syndromes 1-4 (CDLS1, CDLS2, CDLS3, CDLS4)7 | NIPBL, SMC1A, SMC3, RAD21 (122470, 300590, 610759, 614701) |
| Developmental and epileptic encephalopathy 94 (DEE94) | CHD2 (615369) |
| Down syndrome | Chr21 trisomy (190685) |
| Dystonia 28, Childhood-onset (DYT28) | KMT2B (617284) |
| Floating-Harbour syndrome (FLHS) | SRCAP (136140) |
| Gabriele-de Vries syndrome (GADEVS) | YY1 (617557) |
| Genitopatellar syndrome (see also Ohdo syndrome) (GTPTS)8 | KAT6B (606170) |
| Helsmoortel-van der Aa syndrome (HVDAS)9 | ADNP (615873) |
| Hunter McAlpine craniosynostosis syndrome | Chr5q35-qter duplication including NSD1 (601379) |
| Immunodeficiency-centromeric instability- facial anomalies syndromes 1-4 (ICF1, ICF2, ICF3, ICF4)10 | DNMT3B, CDCA7, ZBTB24, HELLS (242860, 614069, 616910, 616911) |
| Intellectual developmental disorder with autism and macrocephaly (IDDAM) | CHD8 (615032) |
| Intellectual developmental disorder with seizures and language delay (IDDSELD) | SETD1B (619000) |
| Intellectual developmental disorder, autosomal dominant 23 (MRD23)11 | SETD5 (615761) |
| Intellectual developmental disorder, autosomal dominant 51 (MRD51)3 | KMT5B (617788) |
| Intellectual developmental disorder, X-linked 93 (XLID93)3 | BRWD3 (300659) |
| Intellectual developmental disorder, X-linked 97 (XLID97) | ZNF711 (300803) |
| Intellectual developmental disorder, X-linked syndromic, Nascimento-type (MRXSN)12 | UBE2A (300860) |
| Intellectual developmental disorder, X-linked, Snyder-Robinson type (MRXSSR) | SMS (309583) |
| Intellectual developmental disorder, X-linked, syndromic, Armfield type (MRXSA) | FAM50A (300261) |
| Intellectual developmental disorder, X-linked, syndromic, Claes-Jensen type (MRXSCJ)3,13 | KDM5C (300534) |
| Kabuki syndrome 1 and 2 (KABUK1, KABUK2) | KMT2D, KDM6A (147920, 300867) |
| Kabuki syndrome 2 (KABUK2)14 | KDM6A (300867) |
| KBG Syndrome (KBGS)11 | ANKRD11 (148050) |
| KDM2B-related syndrome | KDM2B (609078) |
| Kleefstra syndrome 1 (KLEFS1) | EHMT1 (610253) |
| Klinefelter Syndrome | XXY |
| Koolen de Vreis syndrome (KDVS) | KANSL1 (610443) |
| Luscan-Lumish syndrome (LLS) | SETD2 (616831) |
| Menke-Hennekam syndrome 1 and 2 (MKHK1, MKHK2)15 | CREBBP, EP300 (618332, 618333) ID4 domains |
| Nicolaides-Baraitser syndrome (NCBRS)5 | SMARCA2 (601358) |
| Ohdo syndrome, SBBYSS variant (see also Genitopatellar syndrome) (SBBYSS)8 | KAT6B (603736) |
| Phelan-McDermid syndrome (PHMDS)16 | Chr22q13.3 deletion (606232) |
| Potocki-Lupski syndrome (PTLS) | Chr17p11.2 duplication (610883) |
| PRC2 Complex ((Weaver syndrome (WVS) and Cohen-Gibson syndrome (COGIS))17 | EED, EZH2 (617561, 277590) |
| Rahman syndrome (RMNS) | HIST1H1E (617537) |
| Renpenning syndrome (RENS1) | PQBP1 (309500) |
| Rubinstein-Taybi syndrome 1 (RSTS1)18 | CREBBP (180849) |
| Rubinstein-Taybi syndrome 1 and 2 (RSTS1, RSTS2) | CREBBP, EP300 (180849, 613684) |
| Rubinstein-Taybi syndrome 2 (RSTS2)18 | EP300 (613684) |
| Sifrim-Hitz-Weiss syndrome (SIHIWES) | CHD4 (617159) |
| SLC32A1 related disorder | SLC32A1 (616440) |
| Smith-Magenis syndrome (SMS)19 | Chr17p11.2 deletion (182290) |
| Sotos syndrome (SOTOS) | NSD1 (117550) |
| Tatton-Brown-Rahman syndrome (TBRS) | DNMT3A (615879) |
| Velocardiofacial syndrome (VCFS) | Chr22q11.2 deletion (192430) |
| White-Sutton syndrome (WHSUS) | POGZ (616364) |
| Wieacker-Wolff Syndrome (WRWF)20 | ZC4H2 (314580) |
| Wiedemann-Steiner syndrome (WDSTS) | KMT2A (605130) |
| Williams-Beuren region duplication syndrome | Chr7q11.23 duplication (609757) |
| Williams-Beuren syndrome (WBS) | Chr7q11.23 deletion (194050) |
| Witteveen-Kolk syndrome (WITKOS) | SIN3A (613406) |
| Wolf-Hirschhorn syndrome (WHS)21 | Chr4p16.13 deletion, NSD2 (194190) |

1. Patients with other BAFopathy genes may be detected, but not confirmed.
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.
8. GTPTS and SBBYSS are both caused by KAT6B mutations. Both are reported 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.