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|  | | **Genomic Medicine Service**  **Rare Disease DNA Methylation Array Request**  (DOC5741 revision 2) | | | | | **Lab No:**  **(Lab Use only)** | LabNumber | |
| **Patient Details** | | | | | **Referring Clinician / Healthcare Professional** | | | | |
| **NHS No:** | NHS No | **D.O.B:** | DOB | | **Consultant:**  (in full) | | Consultant | | |
| **Surname:** | Surname | **Forename:** | Forename | | **Email / Tel:** | | Email | | |
| **Patient’s address:** | Address | **Biological Sex:** | Sex | | **Hospital / Surgery:**  (in full) | | Hospital | | |
| **Ethnicity:** | Ethnicity | | **Department** | | Department | | |
| **Postcode:** | Postcode | **Hospital No:** | HospitalNo | | **Requested by / Cc**  **Report to:** | | RequestedBy | | |
| **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\*:** | | | SampleDate | | |
| **Taken By:** | | TakenBy | | **Sample Ref:** | SampleRef |
| **Further Details:** | | 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. | | | | | | | | | |
| **Previously detected variants of interest (please provide details according to HGVS nomenclature)**  PreviousVariants | | | | | | | | | |
| **Clinically suspected diagnosis (Please provide OMIM disease ID)**  Diagnosis | | | | | | | | | |
| **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](mailto:mft.epipro.nwglh-lab@nhs.net)) | | | | | | | | | |
| ClinicalDetails | | | | | | | | | |
| **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** | | |  |  |

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| **Disorders detectable by this array** | |
| **Disease/Disorder** | **Causative gene or region (OMIM#)** |
| Alpha-thalassemia mental retardation syndrome (ATRX) | *ATRX* (300032) |
| Arboleda-Tham syndrome (formerly MRD32) (MRD32) | *KAT6A* (616268) |
| Armfield XLID (MRXSA) | *FAM50A* (300261) |
| Autism, susceptibility to, 18 (AUTS18) | *CHD8* (615032) |
| BAFopathies: Coffin-Siris 1-4 (CSS1-4) & Nicolaides-Baraitser (NCBRS) syndromes (BAFopathy)**1** | *ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCA2* (135900,614607,614608,614609,601358) |
| Beck-Fahrner syndrome (BEFAHRS)**2,3** | *TET3* (618798) |
| Blepharophimosis Intellectual disability SMARCA2 Syndrome (BISS) | *SMARCA2* (PMID:32694869) |
| Börjeson-Forssman-Lehmann syndrome (BFLS) | *PHF6* (301900) |
| Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant (ADCADN) | *DNMT1* (604121) |
| CHARGE syndrome (CHARGE) | *CHD7* (214800) |
| Chr16p11.2 deletion syndrome (Chr16p11.2del ) | Chr16p11.2del (611913) |
| Coffin-Siris syndrome-4 (CSS4\_c.2650)**4** | *SMARCA4* (614609) |
| Coffin-Siris syndrome-9 (CSS9) | *SOX11* (615866) |
| PRC2 complex (Weaver (WVS) and Cohen-Gibson syndrome (COGIS))5 | *EZH2* (277590), *EED* (617561) |
| Cornelia de Lange syndrome (CdLS)**6** | *NIPBL, RAD21, SMC3, SMC1A* (122470) |
| Down syndrome (Down) | Chr21 trisomy (190685) |
| Dystonia-28 (DYT28) | *KMT2B* (617284) |
| Epileptic encephalopathy, childhood-onset (EEOC) | *CHD2* (615369) |
| Floating Harbour syndrome (FLHS) | *SRCAP* (136140) |
| Genitopatellar syndrome (GTPTS)**7** | *KAT6B* (606170) |
| Helsmoortel-van der Aa syndrome (ADNP)**8** | *ADNP* (615873) |
| Hunter McAlpine craniosynostosis syndrome (HMA) | Chr5q35-qter duplication (601379) |
| Immunodeficiency-centromeric instability-facial anomalies syndromes 1-4 (ICF1-4)**9** | *DNMT3B, CDCA7, ZBTB24, HELLS* (242860, 614069, 616910, 616911) |
| Intellectual developmental disorder with seizures and language delay (IDDSELD) | *SETD1B* (619000) |
| Kabuki syndrome 1 and 2 (Kabuki) | *KMT2D, KDM6A* (147920,300867) |
| KDM2B-related syndrome (KDM2B) | *KDM2B* (NA) |
| KDM4B-related syndrome (KDM4B) | *KDM4B* (NA) |
| Kleefstra syndrome 1 (Kleefstra) | *EHMT1* (610253) |
| Koolen de Vreis syndrome (KDVS) | *KANSL1* (610443) |
| Luscan-Lumish syndrome (LLS) | *SETD2* (616831) |
| Menke-Hennekam syndrome 1 & 2 (MKHK1/MKHK2)**10** | *CREBBP, EP300* (618332, 618333) |
| Mental retardation, autosomal dominant 23 (MRD23) | *SETD5* (615761) |
| Mental retardation, autosomal dominant 51 (MRD51)**2** | *KMT5B* (617788) |
| Mental retardation, X-linked 93 (MRX93)**2** | *BRWD3* (300659) |
| Mental retardation, X-linked 97 (MRX97) | *ZNF711* (300803) |
| Mental retardation, X-linked syndromic, Nascimento-type (MRXSN) | *UBE2A* (300860) |
| Mental retardation, X-linked, syndromic, Christianson Type (MRXSCH) | *SLC9A6* (300243) |
| Mental retardation, X-linked, syndromic, Claes-Jensen type (MRXSCJ)**2** | *KDM5C* (300534) |
| Myopathy, lactic acidosis, and sideroblastic anemia-1 (MLASA2) | *YARS2* (600462) |
| Ohdo syndrome, SBBYSS variant (see also Genitopatellar syndrome) (SBBYSS) | *KAT6B* (603736) |
| Phelan-McDermid syndrome (PHMDS) | Chr22q13.3del (SHANK3) (606232) |
| Rahman syndrome (RMNS) | *HIST1H1E* (617537) |
| Renpenning syndrome (RENS1) | *PQBP1* (309500) |
| Rubinstein-Taybi syndrome 1 and 2 (RSTS1, RSTS2)11 | *CREBBP*, *EP300* (180849, 613684) |
| Sotos syndrome 1 (Sotos) | *NSD1* (117550) |
| Tatton-Brown-Rahman syndrome (TBRS) | *DNMT3A* (615879) |
| Velocardiofacial syndrome (VCFS) | Chr22q11.2\_del (192430) |
| Wiedemann-Steiner syndrome (WDSTS) | *KMT2A* (605130) |
| Williams-Beuren deletion syndrome (Chr7q11.23 deletion syndrome) (WBS)**12** | Chr7q11.23 deletion (194050) |
| Williams-Beuren region duplication syndrome (Chr7q11.23 duplication syndrome)**12** | Chr7q11.23 duplication (609757) |
| Wolf-Hirschhorn syndrome (WHS) | Chr4p16.13 deletion (194190) |
| Fragile X syndrome (FXS)13 | TNR */ FMR1* (300624) |
| Mental retardation, FRA12A type (DIP2B) | TNR / *DIP2B* (136630) |
| Angelman syndrome (Angelman) | ID / *UBE3A* (105830) |
| Beckwith-Wiedemann syndrome (BWS) | ID / 11p15 (ICR1, KCNQ1OT1, CDKN1C) (130650) |
| Kagami-Ogatta syndrome (KOS) | ID / 14q32 (145410) |
| Prader-Willi syndrome (PWS) | ID / 15q11 (SNRPN, NDN) (176270) |
| Silver Russel syndrome 1 (SRS1) | ID / 11p15.5 (180860) |
| Silver Russel syndrome 2 (SRS2) | ID / 7p11.2 (618905) |
| Temple syndrome (Temple) | ID / 14q32 (616222) |

1 Patients with other BAFopathy genes may be detected, but not confirmed in this test.

2 Healthy carriers and those with incomplete penetrance are detectable.

3 Patients with biallelic variants are distinguishable from those with monoallelic variants.

4 Only for variants near c.2650. No separate episignature due to too few samples however these samples cluster separately from other BAFopathy/CSS4 samples.

5 Shared signatures between PRC2 complex syndromes WVS and COGIS.

6 Male CdLS5 patients (*HDAC8* mutations) may be detected, but not confirmed in our experiments.

7 GTPTS and SBBYSS are both caused by *KAT6B* mutations. We will report both regardless of which one is requested.

8 ADNP has two distinct signatures depending on where in the gene the mutation occurs. HVDAS\_T signature includes mutations that occupy the N- and C-terminus of the gene and HVDAS\_C includes mutations in the central region of the gene including the nuclear localization signal of the protein approximately c.2000-2340.

9 ICF1 exhibits one signature while ICF 2, 3 and 4 exhibit a separate, common signature.

10 Only for domains IDR4 and ZZ.

11 Separate RSTS1 and RSTS2 signatures replacing the combined RSTS signature from EpiSign v2.

12 The two Chr7q11.23 deletion/duplication syndromes exhibit symmetrical increased/decreased DNA methylation signatures, respectively.

13 Females with *FMR1* expansions will not be detected.

The following list of genes have been classified as having reduced sensitivity and more moderate signatures based on signature strength, limited reference cohort size, or types of mutations that have been tested: *CHD8, PHF6, DNMT3B, CDCA7, ZBTB24, HELLS, SETD5, KMT5B, BRWD3, ZNF711, KAT6B, SMS, DNMT3A.*