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Evaluation of DNA Methylation Episignatures for Diagnosis and Phenotype Correlations in 42 Mendelian Neurodevelopmental Disorders

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In the version of this paper originally published, the underlying cause for Hunter McAlpine syndrome was incorrectly described in Table 1. The relevant description has been changed to read "Chr5q35-qter duplication involving *NSD1*" in the updated Table 1 reflected here. The authors apologize for this error.

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Table 1. Description of the Study Cohort

Syndrome/Episignature	Abbreviation	Underlying Genes	Phenotype MIM Number	Training Cohort	Testing Cohort	Episignature Detected?
ADNP syndrome—5′ and 3′ terminal ends	ADNP_T	*ADNP* (outside c.2000-2340)	615873	14	5	yes
ADNP syndrome—central	ADNP_C	*ADNP* (c.2000-2340)	615873	10	3	yes
alpha-thalassemia mental retardation syndrome	ATRX	*ATRX*	301040	13	5	yes
autism, susceptibility to, 18	AUTS18[a]	*CHD8*	615032	5	0	yes
BAFopathies: Coffin-Siris 1–4 (CSS1–4) and Nicolaides-Baraitser (NCBRS) syndromes	BAFopathy[a]	*ARID1A*[a], *ARID1B, SMARCB1, SMARCA4, SMARCA2*	614607, 135900, 614609, 614608, 601358	50	19	yes
Börjeson-Forssman-Lehmann syndrome	BFLS[a]	*PHF6*	301900	4	0	yes
cerebellar ataxia, deafness, and narcolepsy, autosomal dominant	ADCADN	*DNMT1*	604121	5	0	yes
CHARGE syndrome	CHARGE	*CHD7*	214800	45	15	yes
Chr7q11.23 duplication syndrome	Dup7	Chr7q11.23 duplication	609757	8	2	yes
mental retardation, X-linked, syndromic, Claes-Jensen type (Claes-Jensen syndrome)	CJS	*KDM5C*	300534	26	8	yes
Cornelia de Lange syndrome 1–4	CdLS	*NIPBL, RAD21, SMC3, SMC1A*	122470, 614701, 610759, 300590	31	10	yes
Down syndrome	Down	Chr21 trisomy	190685	29	10	yes
epileptic encephalopathy, childhood-onset	EEOC[a]	*CHD2*	615369	5	0	yes
Floating-Harbor syndrome	FHS	*SRCAP*	136140	15	5	yes
genitopatellar syndrome	GTPTS	*KAT6B*	606170	5	0	yes
Hunter McAlpine syndrome	HMA[a]	Chr5q35-qter duplication involving *NSD1*	601379	4	0	yes
immunodeficiency-centromeric instability-facial anomalies syndrome 1	ICF1	*DNMT3B*	242860	8	0	yes
immunodeficiency-centromeric instability-facial anomalies syndrome 2–4	ICF2_3_4	*CDCA7, ZBTB24, HELLS*	614069, 616910, 616911	7	0	yes
Kabuki syndrome 1 and 2	Kabuki[a]	*KMT2D, KDM6A*[a]	147920, 300867	66	21	yes
Kleefstra syndrome 1	Kleefstra1[a]	*EHMT1*	610253	15	5	yes
Koolen de Vreis syndrome	KDVS[a]	*KANSL1*	610443	6	0	yes
mental retardation, autosomal dominant 51	MRD51[a]	*KMT5B*	617788	5	0	yes
mental retardation, X-linked 93	MRX93[a]	*BRWD3*	300659	5	0	yes
mental retardation, X-linked 97	MRX97[a]	*ZNF711*	300803	13	4	yes
mental retardation, X-linked syndromic, Nascimento-type	MRXSN[a]	*UBE2A*	300860	3	0	yes
mental retardation, X-linked, Snyder-Robinson type	MRXSSR[a]	*SMS*	309583	8	2	yes
Rahman syndrome	RMNS[a]	*HIST1H1E*	617537	6	0	yes
Rubinstein-Taybi syndrome 1 and 2	RSTS[a]	*CREBBP, EP300*	180849, 613684	30	9	yes

(*Continued on next page*)

Table 1. ***Continued***

Syndrome/Episignature	Abbreviation	Underlying Genes	Phenotype MIM Number	Training Cohort	Testing Cohort	Episignature Detected?
SBBYSS syndrome	SBBYSS[a]	*KAT6B*	603736	7	0	yes
SETD1B-related syndrome	SETD1B[a]	*SETD1B*	N/A	8	0	yes
Sotos syndrome	Sotos	*NSD1*	117550	47	15	yes
Tatton-Brown-Rahman syndrome	TBRS[a]	*DNMT3A*	615879	10	4	yes
Wiedemann-Steiner syndrome	WDSTS[a]	*KMT2A*	605130	12	4	yes
Williams syndrome	Williams	Chr7q11.23 deletion	194050	15	6	yes
Cornelia de Lange syndrome 5 (females only)	CdLS5	*HDAC8*	300882	8	N/A	no
FG syndrome 1	FG1[a,b]	*MED12*	305450	9	N/A	no
Glass syndrome	Glass[a,b]	*SATB2*	612313	9	N/A	no
KMT2C-related syndrome*	KMT2C[a,b,c]	*KMT2C*	617768	4	N/A	no
neurodevelopmental disorder with coarse facies and mild distal skeletal abnormalities	NEDCFSA[a,b]	*KDM6B*	618505	5	N/A	no
Rett syndrome	Rett	*MECP2*	312750	36	N/A	no
Siderius-type X-linked syndromic mental retardation	MRXSSD[a,b]	*PHF8*	300263	9	N/A	no
Smith-Magenis syndrome	SMS[a,b]	*RAI1*	309583	15	N/A	no

[a]Indicates that these disorders (or some of their subtypes) were not evaluated in previous studies.
[b]Indicates cohorts with no evidence of a reproducible episignature; this is potentially due to small sample size. A possibility of an episignature is not completely ruled out, and reanalysis using larger sample sizes is warranted.
[c]The OMIM database, at the time of this study, has indicated that subjects with *KMT2C* mutations may be said to have "Kleefstra 2" syndrome. The DNA methylation signature found in Kleefstra 1 (caused by *EHMT1*), however, is completely absent in these subjects. It is acknowledged that these subjects have a distinct phenotype from Kleefstra syndrome and a name change is currently in process with OMIM. The numbers in the testing and training cohort columns indicate the sample counts available for each condition in each category. For cohorts with negative findings in the initial assessment, we did not further split the data into testing and training, and thus, the values in the testing column are indicated with N/A (not applicable).