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Resources for Genetics Professionals — Epigenetic Signature Analysis

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An introduction to epigenetic signature analysis and comparison of gene-specific genome-wide methylation analysis and epigenetic modifications to specific regions of the genome

I. Introduction to Epigenetic Modifications

All human nucleated cells have a nuclear genome (sequence of DNA nucleotides) that encodes the proteins and other gene products responsible for the development of a single-cell zygote into an embryo and then a complex multicellular organism. This developmental process requires that the nuclear genome control the following:

- The timing of nuclear gene expression during embryonic development
- The location of nuclear gene expression to enable the differentiation of tissues and organs with specialized functions

Control over timing and location of gene expression occurs through epigenetic modifications – chemical alterations to DNA nucleotides or proteins that control gene expression but do not alter the DNA sequence itself. Histones, the proteins around which DNA is wound, are often targets for modifications that allow accessibility of the DNA for transcription. (See Table 1 for mechanisms of known epigenetic modifications in normal human cells.)

Table 1. Mechanisms of Known Epigenetic Modifications in Normal Human Development

Target	Epigenetic Modification	Mechanism
DNA	Methylation pattern	Addition of methyl groups near promotors & enhancers to directly **suppress** or indirectly **activate/promote transcription**
	Methylation modification	Addition (methylation) or removal (oxidation) of methyl groups to **refine transcription control**

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Table 1. continued from previous page.

Target	Epigenetic Modification	Mechanism
Histones	Acetylation	Addition of acetyl groups to lysine residues to **activate transcription** by relaxing the interaction between histones & DNA
	ADP ribosylation	Addition of ADP-ribose moieties to **activate transcription**
	Methylation	Addition of methyl groups to lysine residues to **activate** or **suppress transcription**
	Phosphorylation	Addition of phosphate groups to serine, threonine, or tyrosine residues to **activate transcription**
	Sumoylation	Addition of small ubiquitin-related modifier (SUMO) proteins to **suppress transcription**
	Ubiquitination	Addition of ubiquitin or ubiquitin chains to lysine residues to **activate** or **suppress transcription**
Nucleosomes	ATP-dependent chromatin remodeling	Alteration of the nucleosome positioning on DNA & histones present in the nucleosomes & disassembly of nucleosomes to **increase** or **decrease** the **accessibility of DNA for transcription**
Proteins & DNA via noncoding RNA [1]	Methylation (indirect)	Facilitation of modifications to DNA & proteins to **activate** or **suppress transcription**
	Acetylation (indirect)	

1. Of note, noncoding RNAs (ncRNAs) play an important indirect role in controlling epigenetic modifications. Examples include the long ncRNA *Xist* (which coats the inactive X chromosome marking it for methylation) and small ncRNAs including siRNAs, miRNAs and piRNAs (which regulate proteins such as DNA methyltransferases, methyl CpG binding proteins, and histone methyl and acetyl transferases).

II. Epigenetic Modifications to Specific Regions of the Genome

Epigenetic modifications that occur early in embryogenesis to specific regions of the genome result in imprinting, the process by which maternally and paternally derived regions of chromosomes are uniquely chemically modified, leading to different expression of a certain gene or genes depending on their parental origin. Patterns of gene expression and repression vary between imprinted regions on a chromosome. DNA methylation is thought to be the principal mechanism of imprinting.

Genetic Alterations That Affect Epigenetic Modifications to Specific Regions of the Genome

Disease-associated alterations affecting methylation patterns in specific regions of the genome (see Table 2) include:

- Disruption of normal imprinting at a specific chromosome locus (e.g., heterozygous deletions or duplications of an imprinted region, uniparental disomy, and pathogenic variants that alter an imprinting control region, thereby disrupting imprint reprogramming during gametogenesis);
- Hypermethylation (silencing) of an abnormally expanded repeat region;
- Acquired promoter methylation of tumor suppressor genes; and
- Skewed X-chromosome inactivation in females due to or in the presence of a disease-causing variant on one X chromosome.

An assay designed to detect the DNA methylation pattern at a specific chromosome locus (e.g., methylation-sensitive multiplex ligation probe analysis [MS-MLPA], methylation-sensitive quantitative PCR [MS-qPCR], Southern blotting using methyl-sensitive DNA restriction enzymes) is necessary to identify epigenetic

imprinting alterations. Identification of an epigenetic imprinting alteration typically requires the clinician to suspect a specific imprinting disorder and order the appropriate diagnostic test:

- **First-tier** testing (ordered based on clinical suspicion) is often a locus-specific DNA methylation assay to determine if an individual has a disorder caused by an abnormal methylation pattern at a specific chromosome locus (e.g., Prader-Willi/Angelman DNA methylation panel).
- **Second-tier** testing may be necessary to identify the cause of the abnormal methylation pattern at a specific chromosome locus (e.g., FISH testing to identify deletion of the Prader-Willi critical region).

Table 2. Disorders with an Abnormal DNA Methylation Pattern at a Specific Chromosome Locus

Chromosome Locus	Disorder	Mechanism(s)
2p21-p16	Lynch syndrome	Hypermethylation of *MSH2* due to adjacent *EPCAM* deletion
3p22.2		Methylation of *MLH1* promoter
4q35	Facioscapulohumeral muscular dystrophy	Hypomethylation of the D4Z4 repeat array due to pathogenic variant of *SMCHD1* or *DNMT3B*
6q24.2	Transient neonatal diabetes mellitus, 6q24 related	Paternal UPD of chr 6
		Paternal 6q24 duplication
		Maternal hypomethylation of *PLAGL1* TSS alt-DMR due to imprinting defect
Chr 7	Silver-Russell syndrome	Maternal UPD of chr 7
11p15.5		Paternal hypomethylation of IC1 at 11p15.5
		Maternal 11p15.5 duplication
	Beckwith-Wiedemann syndrome	Maternal hypomethylation of IC2
		Paternal UPD of 11p15.5
		Maternal hypermethylation of IC1
	Isolated Wilms tumor (See Wilms Tumor Predisposition.)	Paternal UPD of 11p15.5
		Maternal hypermethylation of IC1
		Maternal *H19* DMR deletion
		Maternal *H19* DMR duplication
14q32	Temple syndrome (OMIM 616222)	Maternal UPD of 14q32
	Kagami-Ogata syndrome (OMIM 608149)	Paternal UPD of 14q32
15q11.2-q13	Prader-Willi syndrome	Paternal 15q11.2-q13 deletion
		Maternal UPD of 15q11.2-q13
		Paternal hypermethylation due to imprinting defect
	Angelman syndrome	Maternal 15q11.2-q13 deletion
		Paternal UPD of 15q11.2-q13
		Maternal hypermethylation due to imprinting defect
20q13	Pseudohypoparathyroidism 1B (See Disorders of *GNAS* Inactivation.)	Maternal hypomethylation due to imprinting defect
		Maternal 20q13 deletion
		Paternal UPD of 20q
Chr 20	UPD(20)mat [1]	Maternal UPD of chr 20

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Chromosome Locus	Disorder	Mechanism(s)
Xq27.3	*FMR1*-related disorders	Maternal hypermethylation of *FMR1* promoter caused by abnormal CGG repeat expansion.

chr = chromosome; DMR = differentially methylated region; IC1 = imprinting center 1; IC2 = imprinting center 2; TSS alt = alternative transcription start site; UPD = uniparental disomy
1. Mulchandani et al [2016]

III. Gene-Specific Genome-Wide DNA Methylation Analysis (Epigenetic Signature Analysis)

In contrast to locus-specific DNA methylation analysis, an assay has been developed that detects the DNA methylation pattern at ~1000 different loci across the genome of a specific cell type (e.g., leukocytes). The genome-wide DNA methylation pattern in control individuals was compared to the genome-wide DNA methylation pattern in individuals with disorders known to be associated with alteration of genes that regulate DNA methylation. A unique gene-specific genome-wide DNA methylation pattern ("epigenetic signature") was identified for each of several single-gene disorders that could be distinguished from other known single-gene epigenetic signatures and the reference genome-wide DNA methylation pattern (see Table 3) [Kernohan et al 2016, Butcher et al 2017, Aref-Eshghi et al 2019].

Of note, determination of the so-called "epigenetic signature" for a specific single-gene disorder required DNA methylation analysis of a large number of individuals with known pathogenic variants in a specific gene responsible for the genome-wide epigenetic modifications. This led to the development of epigenetic signature analysis as a method that compares the genome-wide DNA methylation pattern from an individual with the altered DNA methylation pattern characteristic of each gene listed in Table 3 in a specific cell type (e.g., leukocytes).

To date, epigenetic signature analysis may be useful as a **second-tier** test when **first-tier** gene-specific molecular genetic testing has not established a molecular diagnosis. Epigenetic signature analysis is not appropriate as a first-tier test due to the limited number of single-gene disorders with an identified epigenetic signature, to date. In addition, although identification of an epigenetic signature characteristic of one of the genes listed in Table 3 is suggestive of a diagnosis, further gene-specific molecular genetic testing to identify a causative pathogenic variant is recommended to confirm the diagnosis and allow the appropriate family studies.

Table 3. Genes in Which Pathogenic Variants Result in a Gene-Specific Genome-Wide Epigenetic Signature Identified on DNA Methylation Analysis of a Blood Sample

Gene(s)	Disorder	MOI	References
ADNP	*ADNP*-related disorder [1]	AD	Aref-Eshghi et al [2019], Aref-Eshghi et al [2020]
ARID1A *ARID1B* *SMARCA2* *SMARCA4* *SMARCB1*	BAFopathies (*ARID1B*-related disorder, Coffin-Siris syndrome [2], Nicolaides-Baraitser syndrome)	AD	Aref-Eshghi et al [2018], Aref-Eshghi et al [2020]
SOX11	Coffin-Siris syndrome [2]	AD	Levy et al [2021]
ATRX	Alpha-thalassemia X-linked intellectual disability syndrome	XL	Aref-Eshghi et al [2019], Aref-Eshghi et al [2020], Levy et al [2021]
BRWD3	Intellectual developmental disorder, XL 93 (OMIM 300659)	XL	Aref-Eshghi et al [2020], Levy et al [2021]

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	References
CHD2	*CHD2*-related neurodevelopmental disorders	AD	Aref-Eshghi et al [2020], Levy et al [2021]
CHD7	*CHD7* disorder (e.g., CHARGE syndrome)	AD	Butcher et al [2017], Aref-Eshghi et al [2019], Aref-Eshghi et al [2020], Levy et al [2021]
CHD8	*CHD8*-related neurodevelopmental disorder with overgrowth	AD	Aref-Eshghi et al [2020], Levy et al [2021]
CREBB *EP300*	Rubinstein-Taybi syndrome	AD	Aref-Eshghi et al [2020], Levy et al [2021]
DNMT1	*DNMT1*-related disorder	AD	Kernohan et al [2016], Levy et al [2021]
DNMT3A	Tatton-Brown-Rahman syndrome	AD	Aref-Eshghi et al [2020], Smith et al [2021], Levy et al [2021]
DNMT3B	Immunodeficiency-centromeric instability-facial anomalies syndrome 1 (ICF1) (OMIM 242860) [3]	AR	Aref-Eshghi et al [2020], Levy et al [2021]
CDCA7 *HELLS* *ZBTB24*	ICF2 (OMIM 614069), ICF3 (OMIM 616910), ICF4 (OMIM 616911)		
EHMT1	Kleefstra syndrome	AD	Aref-Eshghi et al [2020], Levy et al [2021]
EED *EZH2*	*EED*-related overgrowth, *EZH2*-related overgrowth	AD	Aref-Eshghi et al [2020], Levy et al [2021]
FAM50A	Intellectual developmental disorder, Armfield type (OMIM 300261)	XL	Levy et al [2021]
H1-4 (formerly *HIST1H1E*)	HIST1H1E syndrome	AD	Burkardt et al [2019], Levy et al [2021]
KANSL1	Koolen-de Vries syndrome	AD	Aref-Eshghi et al [2020], Cherik et al [2022], Levy et al [2021]
KAT6A	Arboleda-Tham syndrome (OMIM 616268)	AD	Levy et al [2021]
KAT6B	Genitopatellar syndrome [4]	AD	Aref-Eshghi et al [2019], Aref-Eshghi et al [2020], Levy et al [2021]
	Say-Barber-Biesecker-Young-Simpson syndrome [4]		
KDM2B	*KDM2B*-related syndrome		Yokotsuka-Ishida et al [2021], Levy et al [2021]
KDM4B	Intellectual developmental disorder, AD 65 (OMIM 619320)	AD	Levy et al [2021]
KDM5C	Claes-Jensen syndrome (OMIM 300534)	XL	Aref-Eshghi et al [2019], Aref-Eshghi et al [2020], Levy et al [2021]
KDM6A KMT2D	Kabuki syndrome	AD	Butcher et al [2017], Aref-Eshghi et al [2019], Aref-Eshghi et al [2020], Levy et al [2021]
KMT2A	Wiedemann-Steiner syndrome	AD	Aref-Eshghi et al [2020], Levy et al [2021]
KMT2B	*KMT2B*-related dystonia	AD	Levy et al [2021]

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	References
KMT5B	Intellectual developmental disorder, AD 51 (OMIM 617788)	AD	Aref-Eshghi et al [2020], Levy et al [2021]
NIPBL *RAD21* *SMC3* *SMC1A*	Cornelia de Lange syndrome [5]	AD/XL [6]	Aref-Eshghi et al [2020], Levy et al [2021]
NSD1	Sotos syndrome	AD	Aref-Eshghi et al [2019], Aref-Eshghi et al [2020], Levy et al [2021]
PHF6	Börjeson-Forssman-Lehmann syndrome (OMIM 301900) [7]	XL	Aref-Eshghi et al [2020], Levy et al [2021]
PQBP1	Renpenning syndrome (OMIM 309500)	XL	Levy et al [2021]
SETD1B	*SETD1B*-related neurodevelopmental disorder	AD	Aref-Eshghi et al [2020], Levy et al [2021]
SETD2	*SETD2* neurodevelopmental disorders	AD	Levy et al [2021]
SETD5	Intellectual developmental disorder, AD 23 (OMIM 615761)	AD	Levy et al [2021]
SMS	Snyder-Robinson syndrome	XL	Aref-Eshghi et al [2020], Levy et al [2021]
SRCAP	Floating-Harbor syndrome	AD	Aref-Eshghi et al [2019], Aref-Eshghi et al [2020], Levy et al [2021]
TET3	Beck-Fahrner syndrome		Levy et al [2021]
UBE2A	Intellectual disability disorder, Nascimento-type (OMIM 300860)	XL	Aref-Eshghi et al [2020], Levy et al [2021]
YARS2	Myopathy, lactic acidosis, and sideroblastic anemia 2 (OMIM 613561)	AR	Levy et al [2021]
YY1	Gabriele-de Vries syndrome	AD	Levy et al [2021]
ZNF711	Intellectual developmental disorder, XL 97 (OMIM 300803)	XL	Aref-Eshghi et al [2020], Levy et al [2021]

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Two distinct gene-specific genome-wide DNA methylation patterns were identified in individuals with an *ADNP* pathogenic variant: The pattern associated with *ADNP* pathogenic variants between c.2000 and c.2340 differed from that of pathogenic variants outside c.2000-2340 [Aref-Eshghi et al 2019].

2. Rarely, individuals with clinical features of Coffin-Siris syndrome have been found to have biallelic pathogenic variants in *ARID2, DPF2, PHF6, SMARCC2, SMARCE1,* or *SOX4*; To date, distinct epigenetic signatures have not been reported in individuals with Coffin-Siris syndrome attributed to pathogenic variants in one of these genes.

3. The DNA methylation pattern in individuals with ICF1 could be fully distinguished from the DNA methylation pattern of those with ICF2, ICF3, and ICF4 [Aref-Eshghi et al 2020].

4. Individuals with the allelic disorders genitopatellar syndrome and Say-Barber-Biesecker-Young-Simpson syndrome were found to have distinct epigenetic methylation patterns.

5. To date, individuals with Cornelia de Lange syndrome attributed to pathogenic variants in *BRD4,* or *HDAC8* have not been found to have a distinct epigenetic signature.

6. NIPBL-, *RAD21*-, and *SMC3*-Cornelia de Lange syndrome are inherited in an autosomal dominant manner; *SMC1A*-Cornelia de Lange syndrome is inherited in an X-linked manner.

7. To date, a distinct epigenetic signature has been identified in affected males; affected heterozygous females have not been found to have the same epigenetic pattern [Kerkhof et al 2022]

Examples of Clinical Use of Gene-Specific Genome-Wide Epigenetic Signature Analysis

An individual with clinical features suggestive of *CHD7*-related disorder (e.g., CHARGE syndrome) without an identified *CHD7* pathogenic variant was found to have a gene-specific genome-wide DNA methylation pattern consistent with the epigenetic signature of *CHD7* disorder – further supporting (but not confirming) the clinical diagnosis.

Another individual with a *CHD7* variant of uncertain significance (VUS) was found to have a gene-specific genome-wide DNA methylation pattern consistent with the epigenetic signature of *ADNP*-related intellectual disability and autism spectrum disorder, a diagnosis subsequently confirmed by molecular genetic testing [Aref-Eshghi et al 2019].

What Are the Clinical Uses of Gene-Specific Genome-Wide Epigenetic Signature Analysis in Single-Gene Disorders?

Gene-specific genome-wide epigenetic signature analysis can suggest a molecular diagnosis in individuals with clinical features of one of the disorders in Table 3 when:

- A VUS has been identified on molecular genetic testing;
- A pathogenic variant was not identified because the molecular genetic testing methodology was not designed to detect variants such as large duplications and/or deletions, noncoding variants, or mosaic variants;
- A pathogenic variant was not identified in an individual with clinical features suggestive of more than one disorder listed in Table 3 (e.g., *CHD7* disorder and Kabuki syndrome) [Butcher et al 2017].

What Are the Current Limitations of Gene-Specific Genome-Wide Epigenetic Signature Analysis in Single-Gene Disorders?

Epigenetic signature analysis has only been reported for the diagnosis of disorders that have a known distinct genome-wide epigenetic signature (see Table 3). Additional single-gene disorders with genome-wide epigenetic signatures may exist; however, data to date have not been sufficient to delineate them.

Of note, the epigenetic signature identified in males with an X-linked disorder may or may not be present in affected or unaffected females with a heterozygous pathogenic variant associated with the disorder [Kerkhof et al 2022].

Importantly, epigenetic signature analysis requires a specific sample type as DNA methylation patterns vary by cell and tissue type. For example, DNA from amniocytes, chorionic villi, and/or fibroblasts may not be appropriate to test for a gene-specific genome-wide epigenetic signature previously characterized only in peripheral blood samples. (Because DNA banking methods do not interfere with analysis of epigenetic signature from peripheral blood, DNA banked from a blood sample can be used for gene-specific genome-wide epigenetic signature analysis previously characterized in blood samples [Hjorthaug et al 2018].)

Individuals mosaic for a disorder with a known epigenetic signature may not be identified on epigenetic signature analysis if the pathogenic variant is either absent or present at a very low level in peripheral leukocytes. Testing affected tissue may not be helpful if a known epigenetic signature has not been reported or described for the affected tissue.

Possible Future Developments

Despite identification of known mechanisms of genome-wide epigenetic modification (Table 1), DNA methylation is, to date, the only method for which sufficient data exist to enable construction of a reference genome-wide pattern of epigenetic modification. It is anticipated that in the future, unique genome-wide epigenetic signatures associated with variants in additional genes will likely be identified. New assays may also be developed to identify other mechanisms associated with gene-specific genome-wide epigenetic modification.

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References

Aref-Eshghi E, Bend EG, Colaiacovo S, Caudle M, Chakrabarti R, Napier M, Brick L, Brady L, Carere DA, Levy MA, Kerkhof J, Stuart A, Saleh M, Beaudet AL, Li C, Kozenko M, Karp N, Prasad C, Siu VM, Tarnopolsky MA, Ainsworth PJ, Lin H, Rodenhiser DI, Krantz ID, Deardorff MA, Schwartz CE, Sadikovic B. Diagnostic utility of genome-wide DNA methylation testing in genetically unsolved individuals with suspected hereditary conditions. Am J Hum Genet. 2019;104:685–700. PubMed PMID: 30929737.

Aref-Eshghi E, Bend EG, Hood RL, Schenkel LC, Carere DA, Chakrabarti R, Nagamani SCS, Cheung SW, Campeau PM, Prasad C, Siu VM, Brady L, Tarnopolsky MA, Callen DJ, Innes AM, White SM, Meschino WS, Shuen AY, Paré G, Bulman DE, Ainsworth PJ, Lin H, Rodenhiser DI, Hennekam RC, Boycott KM, Schwartz CE, Sadikovic B. BAFopathies' DNA methylation epi-signatures demonstrate diagnostic utility and functional continuum of Coffin-Siris and Nicolaides-Baraitser syndromes. Nat Commun. 2018;9:4885. PubMed PMID: 30459321.

Aref-Eshghi E, Kerkhof J, Pedro VP, Groupe DI. France, Barat-Houari M, Ruiz-Pallares N, Andrau JC, Lacombe D, Van-Gils J, Fergelot P, Dubourg C, Cormier-Daire V, Rondeau S, Lecoquierre F, Saugier-Veber P, Nicolas G, Lesca G, Chatron N, Sanlaville D, Vitobello A, Faivre L, Thauvin-Robinet C, Laumonnier F, Raynaud M, Alders M, Mannens M, Henneman P, Hennekam RC, Velasco G, Francastel C, Ulveling D, Ciolfi A, Pizzi S, Tartaglia M, Heide S, Héron D, Mignot C, Keren B, Whalen S, Afenjar A, Bienvenu T, Campeau PM, Rousseau J, Levy MA, Brick L, Kozenko M, Balci TB, Siu VM, Stuart A, Kadour M, Masters J, Takano K, Kleefstra T, de Leeuw N, Field M, Shaw M, Gecz J, Ainsworth PJ, Lin H, Rodenhiser DI, Friez MJ, Tedder M, Lee JA, DuPont BR, Stevenson RE, Skinner SA, Schwartz CE, Genevieve D, Sadikovic B. Evaluation of DNA Methylation Episignatures for Diagnosis and Phenotype Correlations in 42 Mendelian Neurodevelopmental Disorders. Am J Hum Genet. 2020;106:356–70. PubMed PMID: 32109418.

Burkardt DD, Zachariou A, Loveday C, Allen CL, Amor DJ, Ardissone A, Banka S, Bourgois A, Coubes C, Cytrynbaum C, Faivre L, Marion G, Horton R, Kotzot D, Lay-Son G, Lees M, Low K, Luk HM, Mark P, McConkie-Rosell A, McDonald M, Pappas J, Phillipe C, Shears D, Skotko B, Stewart F, Stewart H, Temple IK, Mau-Them FT, Verdugo RA, Weksberg R, Zarate YA, Graham JM, Tatton-Brown K. HIST1H1E heterozygous protein-truncating variants cause a recognizable syndrome with intellectual disability and distinctive facial gestalt: A study to clarify the HIST1H1E syndrome phenotype in 30 individuals. Am J Med Genet A. 2019;179:2049–55. PubMed PMID: 31400068.

Butcher DT, Cytrynbaum C, Turinsky AL, Siu MT, Inbar-Feigenberg M, Mendoza-Londono R, Chitayat D, Walker S, Machado J, Caluseriu O, Dupuis L, Grafodatskaya D, Reardon W, Gilbert-Dussardier B, Verloes A, Bilan F, Milunsky JM, Basran R, Papsin B, Stockley TL, Scherer SW, Choufani S, Brudno M, Weksberg R. CHARGE and Kabuki syndromes: gene-specific DNA methylation signatures identify epigenetic mechanisms linking these clinically overlapping conditions. Am J Hum Genet. 2017;100:773–88. PubMed PMID: 28475860.

Cherik F, Reilly J, Kerkhof J, Levy M, McConkey H, Barat-Houari M, Butler KM, Coubes C, Lee JA, Le Guyader G, Louie RJ, Patterson WG, Tedder ML, Bak M, Hammer TB, Craigen W, Démurger F, Dubourg C, Fradin M, Franciskovich R, Frengen E, Friedman J, Palares NR, Iascone M, Misceo D, Monin P, Odent S, Philippe C, Rouxel F, Saletti V, Strømme P, Thulin PC, Sadikovic B, Genevieve D. DNA methylation episignature in Gabriele-de Vries syndrome. Genet Med. 2022;24:905–14. PubMed PMID: 35027293.

Hjorthaug HS, Gervin K, Mowinckel P, Munthe-Kaas MC. Exploring the influence from whole blood DNA extraction methods on Infinium 450K DNA methylation. PLoS One. 2018;13:e0208699. PubMed PMID: 30540848.

Kerkhof J, Squeo GM, McConkey H, Levy MA, Piemontese MR, Castori M, Accadia M, Biamino E, Della Monica M, Di Giacomo MC, Gervasini C, Maitz S, Melis D, Milani D, Piccione M, Prontera P, Selicorni A, Sadikovic B, Merla G. DNA methylation episignature testing improves molecular diagnosis of Mendelian chromatinopathies. Genet Med. 2022;24:51–60. PubMed PMID: 34906459.

Kernohan KD, Cigana Schenkel L, Huang L, Smith A, Pare G, Ainsworth P. Care4Rare Canada Consortium, Boycott KM, Warman-Chardon J, Sadikovic B. Identification of a methylation profile for DNMT1-associated autosomal dominant cerebellar ataxia, deafness, and narcolepsy. Clin Epigenetics. 2016;8:91. PubMed PMID: 27602171.

Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dyment D, Esber N, Fahrner JA, Fleming MD, Genevieve D, Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of Mendelian disorders. HGG Adv. 2021;3:100075. PubMed PMID: 35047860.

Mulchandani S, Bhoj EJ, Luo M, Powell-Hamilton N, Jenny K, Gripp KW, Elbracht M, Eggermann T, Turner CL, Temple IK, Mackay DJ, Dubbs H, Stevenson DA, Slattery L, Zackai EH, Spinner NB, Krantz ID, Conlin LK. Maternal uniparental disomy of chromosome 20: a novel imprinting disorder of growth failure. Genet Med. 2016;18:309–15. PubMed PMID: 26248010.

Smith AM, LaValle TA, Shinawi M, Ramakrishnan SM, Abel HJ, Hill CA, Kirkland NM, Rettig MP, Helton NM, Heath SE, Ferraro F, Chen DY, Adak S, Semenkovich CF, Christian DL, Martin JR, Gabel HW, Miller CA, Ley TJ. Functional and epigenetic phenotypes of humans and mice with DNMT3A Overgrowth Syndrome. Nat Commun. 2021;12:4549. PubMed PMID: 34315901.

Yokotsuka-Ishida S, Nakamura M, Tomiyasu Y, Nagai M, Kato Y, Tomiyasu A, Umehara H, Hayashi T, Sasaki N, Ueno SI, Sano A. Positional cloning and comprehensive mutation analysis identified a novel KDM2B mutation in a Japanese family with minor malformations, intellectual disability, and schizophrenia. J Hum Genet. 2021;66:597–606. PubMed PMID: 33402700.

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