alamya health

A Future Where Precision Medicine is the Standard

DNA Methylation Signatures

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Background

All cells in the human body contain identical genetic material; yet, early in embryonic development, cells differentiate into specialized cell types, tissues, and organs. This differentiation process is directed by epigenetic mechanisms. Epigenetics is the study of how gene activity in cells is regulated without altering the underlying DNA sequence. Epigenetic mechanisms modify DNA and histone proteins to form chromatin—the structural framework for packaging genetic material, and thereby direct gene activity. When chromatin is open, genes are accessible and active, whereas when it is condensed, genes are inaccessible and silenced. The three main processes that regulate chromatin are DNA methylation, histone modifications, and chromatin remodeling. Epigenetic modifications, which are stable and passed down through cell division, define specific gene function in different tissues.

Recent advances have identified “epigenes” that regulate these processes along with pathogenic variants (e.g., mutations) in epigenes that can disrupt normal chromatin function. Such variants cause abnormal gene expression and a range of genetic disorders, particularly growth and/or neurodevelopmental disorders. These are also referred to as epigenetic disorders or chromatinopathies.

DNA methylation testing is a valuable diagnostic tool that looks for distinct, well-established genome-wide methylation patterns (aka methylation signatures or episignatures) and/or localized methylation changes that are characteristic of specific disorders. Methylation testing can help identify genetic disorders even when genome sequencing does not reveal a clear pathogenic variant. Methylation testing can also clarify the pathogenicity of variants of uncertain significance (VUS). Consequently, DNA methylation testing is an integral component of precision medicine that improves diagnostic accuracy and potentially guides treatment decisions for epigenetic disorders.

The table below lists the genes and the associated disorders with robust methylation signatures (i.e., high sensitivity and specificity) that Alamya Health has incorporated into our testing strategy. The Online Mendelian Inheritance in Man (OMIM) number for each disorder is also listed. OMIM is an online encyclopedia of genetic disorders accessible at OMIM. The Alamya Health team updates the gene list based on current scientific knowledge. Relevant resources and references are provided for positive test findings.

Limitations

The absence of a detectable DNA methylation signature does not rule out variant pathogenicity or the presence of a specific genetic disorder. Uncertain results can arise from factors such as tissue mosaicism, tissue type differences, and reduced variant expressivity. Age, and medication status also influence the methylation pattern.

Detection of altered methylation at specific genomic regions or of specific nucleotides (methylation signatures listed below) is considered a clinically reliable test result with high sensitivity and specificity. The

interpretation of methylation testing results relies on the current knowledge. As this knowledge is constantly changing, not all methylation alterations or signatures are yet known. Additionally, limitations of sequencing technologies and of the interpretation parameters can fail to detect methylation alterations of specific genetic disorders.

The term screening is used because not all DNA methylation alterations are screened, and not all DNA methylation signatures can be identified by the testing technology. A 'negative' result greatly reduces the risk to develop one of the DNA methylation disorders screened; it does not completely rule them out. Age, clinical history, and family history also influence risk.

DNA METHYLATION SIGNATURES SCREENED

Gene Symbol	Disease	OMIM Number
ANKRD11	KBG syndrome	148050
ASXL1	Bohring-Opitz syndrome	605039
ASXL2	Shashi-Pena syndrome	617190
CHD8	Intellectual developmental disorder with autism and macrocephaly	615032
CHD7	CHARGE syndrome	214800
DYRK1A	Intellectual developmental disorder, autosomal dominant 7	614104
EED	Cohen-Gibson syndrome	617561
EHMT1	Kleefstra syndrome 1	610253
EZH2	Weaver syndrome	277590
HNRNPK	Au-Kline syndrome	616580
KDM6A	Kabuki syndrome 2	300867
KMT2C	Kleefstra syndrome 2	617768
KMT2D	Kabuki syndrome 1	147920
NSD1	Sotos syndrome	117550
SMARCA2	Nicolaides-Baraitser syndrome	601358
SRCAP	Floating-Harbor syndrome	136140
SRCAP-upstream	Developmental delay, hypotonia, musculoskeletal defects, and behavioral abnormalities	619595
SUZ12	Imagawa-Matsumoto syndrome	606245
Trisomy 21	Down syndrome	190685
16p11.2 del	Chromosome 16p11.2 deletion syndrome, AUTS14A	611913
7q11.23 dup	Chromosome 7q11.23 duplication syndrome	609757
7q11.23 del	Williams-Beuren syndrome	194050

Notes:
ASXL2 variants are classified using *ASXL1* signature
SUZ12 and *EED* variants are classified using *EZH2* signature
KDM6A variants are classified using *KMT2D* signature