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Episignatures of DNA Methylation in Neurodevelopmental Disorders Linked to Large Structural Copy Number Variations

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Introduction

Through their effects on gene dosage, large structural chromosomal deletions and duplications, also known as copy number variants (CNVs), contribute to the pathogenesis of neurodevelopmental disorders (NDDs). This review focuses on our current understanding of genomic disorders that occur in patients with NDDs as a result of large structural chromosome rearrangements, as well as issues with clinical presentation and molecular diagnosis overlapping. We consider the clinical implications and implications of copy number and genomic DNAm testing in patients with suspected genetic NDDs, as well as the implications of epigenetics, specifically DNA methylation (DNAm), in NDDs and genomic disorders. Global methylation episignatures that can be used in the diagnostic process and may shed light on the molecular pathogenesis of genomic disorders are summarized here. Finally, we talk about the possibility of combining DNAm and CNV testing into a single diagnostic test.

Description

A wide range of genetic and phenotypic variations characterize NDDs and their clinical manifestations frequently lack specificity. The etiology of hereditary NDDs is heavily influenced by genetics. From single nucleotide variants (SNVs) to whole chromosome aneuploidies, the size of the genetic mutations that are associated with NDDs varies. Genetic testing frequently includes global genomic screening, such as chromosomal microarray analysis (CMA), exome or whole genome sequencing (WES, WGS), or classically G-banded chromosome karyotyping (karyotyping), due to the observed phenotypic overlap. CMA, which is regarded as the first-tier diagnostic test for patients with NDDs, has been utilized in clinical settings for nearly two decades to identify structural imbalances involving the deletion or duplication of genetic material, which are collectively referred to as copy number variants (CNVs). While some of the first CMAs used bacterial artificial chromosome (BAC) clones in an array-based comparative genomic hybridization (aCGH) that covered the entire genome at intervals of about 1 Mb, more recent platforms that use oligonucleotide or high-resolution single nucleotide polymorphism (SNP) arrays can only resolve a few hundred base pairs. As a result, genomic imbalances with minimum detection sizes of 3–7 Mb that go beyond the resolution of karyotyping are now routinely detected. SNP arrays are designed to determine genotype, structural imbalances, genomic aneuploidy and loss of heterozygosis and offer the highest resolution of commercially available microarrays [1].

Increased resolution and coverage can be achieved by customizing microarray platforms in regions that are clinically relevant and associated with clearly defined genomic syndromes. Clinical microarray platforms have probes equally spaced across the remainder of the genome, referred to as "backbone" coverage, in addition to probe-coverage enriched regions. Since we don't know much about how CNVs outside of protein coding regions affect genes, high probe densities and optimized targeted design are meant to reduce the number of ambiguous findings known as variants of uncertain significance (VUSs). Without altering the DNA sequence, mitotically heritable gene regulatory mechanisms are referred to as epigenetics. Processes that alter chromatin or histones, the proteins that wrap DNA, or covalent modifications in the associated DNA molecule are typically involved in epigenetic regulation of gene expression, which occurs at the level of chromatin. DNAm refers to the process of adding or removing a methyl group from cytosine nucleotides and is the epigenetic modification that has received the most research attention [2].

CpG dinucleotide (CpGs) are the majority of cytosines that are affected by DNA modification and are located close to guanine residues. CpG islands are high-density clusters of CpGs that are frequently associated with gene promoters. DNA hyper methylation is correlated with compact, transcriptionally repressive chromatin, whereas methylated (hypo methylated) CpGs and CpG islands are typically associated with open, transcriptionally accessible chromatin. With the exception of those that are located within CpG islands, the majority of CpGs in the human genome are methylated. Hence, as well as influencing chromatin states and security, disturbances in DNAm examples can change quality articulation. Numerous NDDs are being linked to an increasing number of chromatin and epigenetic regulatory genes. DNAm episignatures, also known as changes in the methylation of the entire genome, are the results of mutations in these genes and are frequently detected in the peripheral blood of patients with these conditions. Histone changes allude to the synthetic adjustment of histone tails by processes including methylation, acetylation, phosphorylation and ubiquitination [3].

Histone tails are protein segments with a loose structure that can mediate interactions between nucleosomes. Their modifications can make chromatin more or less condensed, which has an effect on gene transcription and makes DNA more accessible to other chromatin remodelling factors, like those that affect DNA methylation. Multiple NDDs, such as Kabuki syndrome, which is caused by mutations in the lysine-specific methyltransferase 2D gene (KMT2D), have unique episignatures that have been identified by our group and others. These episignatures are the result of mutations in genes that are associated with histone modification. We have planned episignatures in a few other histone changing qualities including lysine-explicit methyltransferase 2B (KMT2B), set space containing protein 2 (SETD2), creb-restricting protein (CREBBP), lysine acetyltransferase 6A (KAT6A) and lysine demethylase 4B (KDM4B). The so-called "eraser" genes, such as the histone lysine demethylase 5C gene (KDM5C) in Claes–Jensen syndrome, have also been associated with the removal of histone methylation marks and unique episignatures have been reported in these genes. DNAm and histone modifications collaborate to influence chromatin remodelling and gene expression.

DNA methyltransferases (DNMT) are the enzymes that mediate the transfer of the methyl group from S-adenosylmethionine (SAM) to cytosine residues, triggering the DNAm reaction. Mutations in the DNA methyltransferase genes DNMT1, DNMT3A and DNMT3B, which are involved in the establishment and maintenance of DNAm during DNA replication and are referred to as "writers" because they are responsible for the addition of the methyl group to cytosines, have been linked to robust episignatures in NDDs. Mutations in DNMT1 are

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linked to unique episignatures in two disorders: HSNDHL (hereditary sensory neuropathy with dementia and hearing loss) and ADCADN (autosomal dominant cerebellar ataxia, deafness and narcolepsy). On the other hand, loss of function mutations in DNMT3A causes an episignature in Tatton–Brown–Rahman syndrome (TBRS). DNAm's genomic defects are caused by mutations in DNMT3B, which also cause immunodeficiency, centromere instability and facial anomalies (ICF) syndrome. Tet methyl cytosine dioxygenase 3 (TET3), a DNA demethylation gene that opposes DNMT1's writer function, recently displayed a genome-wide DNA hyper methylation episignature [4].

Beck–Fahrner syndrome (BEFAHRS) is caused by mutations in the TET3 catalytic domain, which is highly conserved. BEFAHRS inheritance patterns range from autosomal dominant to recessive. We were able to distinguish affected individuals with mono-allelic and bi-allelic mutations using episignature mapping. Currently, the largest group of epigenetic modifier genes with mapped episignatures are chromatin remodelling genes. For instance, truncating mutations in the SNF2-related CBP activator protein gene (SRCAP) produce an episignature that is unique to Floating-Harbor syndrome. Coffrin–Siris and Nicolaides–Baraitser syndromes (NCBRS), two phenotypically comparable NDDs associated with mutations in subunits of the BAF chromatin remodeling complex (commonly referred to as BAFopathies), share a DNAm episignature, as our group previously demonstrated.

This study confirmed previous findings that these conditions represent a disease spectrum rather than two distinct disorders by describing a shared BAFopathies episignature. In addition, this study suggests that methylation analysis might reveal or provide additional evidence for the "relatedness" of diseases and genes. A new syndrome involving the BAF complex and the SWI/SNF-related matrix-associated, actin-dependent regulator of the chromatin gene (SMARCA2), which has been identified in multiple NCBRS patients, was described in a subsequent study by our group. Individuals with intragenic variants in the helicase domain of the SMARCA2 gene exhibited distinct methylation patterns in comparison to those with pathogenic variants outside the helicase domain, which led to the identification of this new syndrome [5].

Conclusion

Patients with SMARCA2 helicase domain mutations shared a phenotype that was distinct from NCBRS, supporting these findings. In a similar vein, functional studies conducted on yeast revealed a distinct molecular mechanism responsible for these two disorders. We were able to identify two distinct episignatures and uncover functional data to explain the phenotypic differences observed between patients harbouring variants in the same gene by analysing variants from multiple regions within a gene. This led to the discovery of a new syndrome.

Acknowledgement

None.

Conflict of Interest

None.

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