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COMMENT

ZNF711 puts a spell on DNA

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It has been known for a long time that genetic variations beyond the DNA sequence play a role in genomic regulation. So-called epigenetic variations are usually defined as phenomena that are independent of underlying changes in DNA sequence and that are inheritable or otherwise may persist during mitosis. One of the best-known epigenetic examples includes the addition of a methyl group to the Cytosine base preceding a Guanine to form a 5-Methylcytosine. This dinucleotide, commonly referred to as CpG is usually methylated, apart from when these occur in so-called CpG islands: a stretch of DNA with a higher-than-expected density of CpG dinucleotides. These CpG islands typically occur at the transcription start sites (TSS) of genes involved in routine cellular functions. The methylation of such CpG islands leads to long-term silencing of the associated genes.

Over the last decade, it has been increasingly recognized that variations in the methylation patterns between individuals occur spontaneously [1]. For instance, promotor hypermethylation may occur that can be associated with disease but can also exist without detectable clinical consequences. A synchronous variation in the methylation pattern of a set of sequential CpG nucleotides is called an epimutation. Intriguingly, a subset of monogenic neurodevelopmental disorders have been shown to be associated with a specific and recognizable pattern of epimutations throughout their genome, referred to as an episignature [2]. This episignature is thought to be the consequence of the mutation in the disease-causing gene. In this issue of the European Journal of Human Genetics, a worldwide investigators' collective guided by the US-based Greenwood Genetic Center describes how patients with a mutation in the zinc-finger gene *ZNF711* have one such unique episignature [3]. *ZNF711* is a gene that has been convincingly reported as causative for non-syndromic intellectual disability in 2017 [4]. Because the gene is located on the X-chromosome, the pedigrees can become extensive as unaffected carrier females transmit the mutations to 50% of their affected sons. In their paper, the authors present a total of six pedigrees with a pathogenic *ZNF711* mutation, including one novel multi-generational and three nuclear families in as well as two extended versions of previously reported pedigrees. They subjected 15 patients of these pedigrees along with patients from two previously reported families [4] to array-based methylation profiling and established a pattern of 161 epimutations that clustered away from the controls. Having established an episignature, its robustness was validated by a testing set consisting of a mix of sample replicates and additional patients. The epivariations from the entire testing set clustered convincingly with the patients. Vice versa, patients from two families with variations in *ZNF711* predicted non-pathogenic clustered with controls. Of special interest is the observation that the episignature of an unaffected carrier mother also clustered with controls.

From a diagnostic point of view, this work increases our hopes that the establishment of a recognizable episignature can help discriminate a pathogenic from a benign variant in the DNA sequence. Epivariations can especially be of added value in case of non-syndromic X-linked intellectual disability as for instance caused by *ZNF711* mutations. In such cases, the variations are often inherited from an unaffected carrier mother and the clinical hallmarks of the affected individual are not usually sufficiently discriminative to aid in the clinical diagnosis. On the speculative side, it would be a genetic counselor's dream should the epivariations permit a distinction between affected and non-affected carrier females. This study raises some hope this dream might become a reality, as the epivariations of the unaffected carrier mother clustered with those from the controls. It should be mentioned though that in this study only a single female was included and that due to a lack of affected carrier females, it could only be compared with male patients. Moreover, X-inactivation of the diseased chromosome has not been excluded as a contributing factor to the epigenetic variations observed. Despite these inevitable drawbacks in the study design, epigenetic profiling remains an interesting path to pursue predictions in the clinical status of females carrying a *ZNF711* mutation or in any other disease-causing gene on the X-chromosome.

Surprisingly, the mechanism connecting the causative mutation with the episignatures remains an enigma. In the overwhelming majority of diseases investigated, the mutated gene plays a direct role in DNA modification or chromatin remodeling [2]. In these disorders, it is tempting to speculate that haploinsufficiency of the disease-associated chromatin remodeler affects the establishment of the epigenome, leading to the aberrations observed. However, *ZNF711* is a Krüppel-type zinc-finger, consisting of 11 intact C_2H_2 type zinc-finger domains, a nuclear localization signal and a transactivation acidic domain [5]. Its protein product binds to CpG-island promotors downstream of the TSS and could not be expected to affect the episignature of affected individuals. However, one of its preferential binding partners is the histone H3K9me1/me2 demethylase *PHF8*. Together, these proteins activate, amongst many other genes, the transcription of *KDM5C*, a histone H3K4me2/me3 demethylase [6]. As such, the epivariations could be speculated to be a downstream effect of the absence of *ZNF711* (Fig. 1). Whatever the mechanism behind the *ZNF711* epimutations, it remains a novelty that genes not directly involved in epigenetic processes themselves can leave a genome-wide epigenetic mark when mutated.

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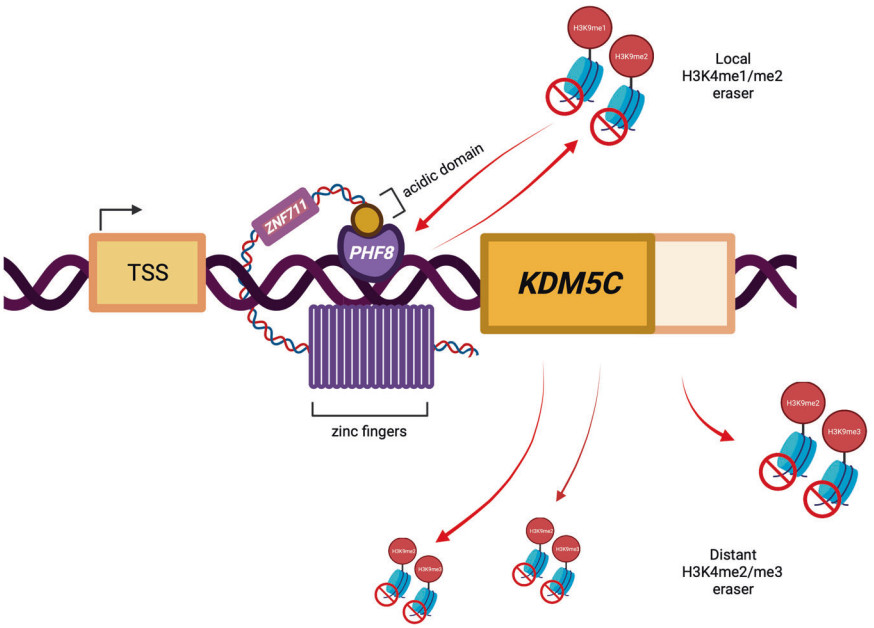

Fig. 1 Graphical representation of how *ZNF711* may affect the episignature. With its zinc fingers, the transcription activator *ZNF711* binds DNA between the transcription and translation imitation start site of its target genes, including the *KDM5C* gene [5]. With its acidic domain, *ZNF711* recruits the eraser *PHF8*, resulting in local removal of the H3K4me1/me2 mark, enhancing transcriptional activation of *KDM5C* [6]. The protein product of *KDM5C* on its turn impacts the epigenetic status of the genome by demethylation of H3K4me2/me3 into H3K4me1. Such changes in histone methylation have an impact on further downstream chromatin remodeling and it can be hypothesized that these changes include the characteristic changes in the episignature as observed in this study [3].

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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