SIN3A Witteveen-Kolk syndrome WITKOS

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Purpose:

Witteveen-Kolk syndrome (WITKOS) is a rare, autosomal dominant neurodevelopmental disorder caused by heterozygous loss-of-function alterations in the SIN3A gene. WITKOS has variable expressivity that commonly overlaps with other neurodevelopmental disorders. In this study, we characterized a distinct DNA methylation epigenetic signature (episignature) distinguishing WITKOS from unaffected individuals as well as individuals with other neurodevelopmental disorders with episignatures and described 9 previously unpublished individuals with SIN3A haploinsufficiency.

Methods:

We studied the phenotypic characteristics and the genome-wide DNA methylation in the peripheral blood samples of 20 individuals with heterozygous alterations in SIN3A. A total of 14 samples were used for the identification of the episignature and building of a predictive diagnostic

biomarker, whereas the diagnostic model was used to investigate the methylation pattern of the remaining 6 samples.

Results:

A predominantly hypomethylated DNA methylation profile specific to WITKOS was identified, and the classifier model was able to diagnose a previously unresolved test case. The episignature was sensitive enough to detect individuals with varying degrees of phenotypic severity carrying SIN3A haploinsufficient variants.

Conclusion:

We identified a novel, robust episignature in WITKOS due to SIN3A haploinsufficiency. This

episignature has the potential to aid identification and diagnosis of individuals with WITKOS.