From methylation to malformation: the role of DNA methylation in the pathogenesis of Klippel-Feil syndrome

Research project objectives:

Congenital vertebral malformations (CVMs) represent a significant global health challenge, resulting in chronic pain and disability. CVMs encompass a heterogeneous group of disorders, manifesting as isolated conditions (hemivertebrae, butterfly vertebra, wedge vertebrae) or as part of rare congenital syndromes (e.g. Klippel-Feil syndrome). CVMs have a multifactorial etiology involving genetic and environmental factors such as maternal drug intake and maternal diseases during pregnancy. Although the molecular basis of some syndromes associated with vertebral defects has been explained, the molecular etiologies of a subset of CVMs (including Klippel-Feil syndrome, congenital scoliosis, and isolated VMs) remain incompletely understood. Therefore, we propose supplementing the molecular framework with a comprehensive whole-genome methylation analysis. The alterations in DNA methylation patterns may serve as a potential link between environmental factors and CVMs.

The main objective of this project is to investigate whole-genome DNA methylation in patients with Klippel-Feil syndrome (KFS). The project continues the ongoing research conducted during the PI's Ph.D. project, "Towards an understanding of the molecular basis of osseous structural vertebral malformations in humans.".

Research project methodology:

The study will involve epigenetic analysis of DNA samples derived from peripheral blood obtained from 16 Polish patients with KFS and 16 healthy controls with the same ethnicity, age, and gender. DNA methylation profiling will be performed using the Infinium Methylation EPIC arrays containing 850,000 methylation sites. Bioinformatic and statistical analyses, employing tools such as R programming, will be conducted to identify differentially methylated regions of the most functional importance. Validation of genome-wide methylation results will be performed using bisulfite pyrosequencing. Integrative analyses will incorporate genomic data (aCGH, NGS, WGS), transcriptomic data (RNA-Seq), chromatin data (4C, ChIP-seq), and epigenomic data (EPIC) derived from the same biological material.

The expected results of the project:

The expected result of the project is an explanation of the role of DNA methylation as an epigenetic factor in the pathogenesis of KFS. We expect that genes within the identified differentially methylated regions will be involved in key biological pathways associated with skeletal formation. Since our methylation studies in KFS are the first globally, the results will be of significant interest to genetics, researchers, and students in the medical and biological fields. Identifying new causes for CVMs represents a step towards improved molecular diagnostics, genetic counseling, and potential treatments, ultimately leading to better patient outcomes and quality of life.