The Journal of Molecular Diagnostics
Volume 23, Issue 7, July 2021, Pages 834-846

Regular article

DNA Methylation Profiling Discriminates between Malignant Pleural Mesothelioma and Neoplastic or Reactive Histologic Mimics

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https://doi.org/10.1016/j.jmoldx.2021.04.002

The diagnosis of malignant pleural mesothelioma (MPM) is challenging because of its potential overlap with other neoplasms or even with reactive conditions. DNA methylation analysis is effective in diagnosing tumors. In the present study, this approach was tested for use in MPM diagnosis. The DNA methylation patterns of a discovery cohort and an independent-validation cohort of MPMs were compared to those of 202 cases representing malignant and benign diagnostic mimics (angiosarcoma, desmoid-type fibromatosis, epithelioid sarcoma, leiomyosarcoma, lung adenocarcinoma, lung squamous cell carcinoma, melanoma, nodular fasciitis, reactive mesothelial hyperplasia, sclerosing fibrous pleuritis, solitary fibrous tumor, and synovial sarcoma). By both unsupervised hierarchical clustering and t-distributed stochastic neighbor embedding analysis, MPM samples in the discovery cohort exhibited a DNA methylation profile different from those of other neoplastic and reactive mimics. These results were confirmed in the independent validation cohort and by *in silico* analysis of the MPM–The Cancer Genome Atlas data set. Copy number variation profiles were also inferred to identify molecular hallmarks of MPM, including *CDKN2A* and *NF2* deletions. Methylation profiling was effective in the diagnosis of MPM, although caution is advised in samples with low tumor cell content.

Supported by German Cancer Aid grant 70112499 (A.v.D.); Italian Ministry for Education, University and Research Programme "Dipartimenti di Eccellenza 2018 to 2022" project grant D15D18000410001 (L.B. and P.C.); Italian Association for Cancer Research investigator grant 2019 23760 (G.V.S.); and a Regione Piemonte Mesothelioma Project "Mesoline: Mesothelioma Pipeline: From the Genome to Innovative Therapeutic Approaches" grant (G.V.S.).

L.B. and L.R. contributed equally to this work.

Disclosures: None declared.