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

Luca Bertero *, † 🕭 🗷, Luisella Righi ‡, Giammarco Collemi *, Christian Koelsche ∮, Yanghao Hou †, Damian Stichel †, ¶, Damiel Schrimpf †, ¶, Uta Flucke ‡, Iver Petersen **, Christian Vokuhl ††, Stefan Fröhling ‡‡, ∰, Paolo Bironzo 📢, Giorgio V. Scagliotti ¶, Paola Cassoni *, Mauro Papotti II, Andreas von Deimling †, ¶

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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



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

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