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53 DEVELOPMENT AND VALIDATION OF A MOLECULAR CLASSIFIER OF MENINGIOMAS

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BACKGROUND: Meningiomas exhibit considerable clinical and biological heterogeneity. We previously identified four distinct molecular groups (immunogenic, NF2-wildtype, hypermetabolic, proliferative) that address much of this heterogeneity. Despite the utility of these groups, the stochasticity of clustering methods and the use of multi-omics data for discovery limits the potential for classifying prospective cases. We sought to address this with a dedicated classifier. METHODS: Using an international cohort of 1698 meningiomas, we constructed and rigorously validated a machine learning-based molecular classifier using only DNA methylation data as input. Original and newly-predicted molecular groups were compared using DNA methylation, RNA sequencing, copy number profiles, whole exome sequencing, and clinical outcomes. RESULTS: We show that group-specific outcomes in the validation cohort are nearly identical to those originally described, with median PFS of 7.4 (4.9-Inf) years in hypermetabolic tumors and 2.5 (2.3-5.3) years in proliferative tumors (not reached in the other groups). Tumors classified as NF2-wildtype had no NF2 mutations, and 51.4% had canonical mutations previously described in this group. RNA pathway analysis revealed upregulation of immune-related pathways in the immunogenic group, metabolic pathways in the hypermetabolic group and cell-cycle programs in the proliferative group. Bulk deconvolution similarly revealed enrichment of macrophages in immunogenic tumours and neoplastic cells in hypermetabolic and proliferative tumours with similar proportions to those originally described. CONCLUSIONS: Our DNA methylation-based classifier, which is publicly available for immediate clinical use, recapitulates the biology and outcomes of the original molecular groups as assessed using multiple metrics/platforms that were not used in its training.