

# BRAIN PATHOLOGY










## Brain Pathology

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## Genetics of Glioma Progression and the Definition of Primary and Secondary Glioblastoma

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### ABSTRACT



Glioblastoma multiforme, the most malignant human brain tumor, may develop de novo (primary glioblastoma) or through progression from low-grade or anaplastic astrocytoma (secondary glioblastoma). We present evidence that these subtypes of glioblastoma constitute distinct disease entities which evolve through different genetic pathways, affect patients at different age and are likely to differ in prognosis and response to therapy. Primary glioblastomas develop in older patients (mean, 55 years) and typically show EGFR overexpression or, less frequently, MDM2 overexpression and pi6 deletion. Secondary glioblastomas develop in younger patients (mean, 40 years) and frequently contain TP53 mutations and, less consistently, loss of DCC expression. Although primary and secondary glioblastomas are considered to be histologically indistinguishable, we found that the pattern and pathogenesis of necrosis are different, large areas of ischaemic necrosis surrounded by Fas expressing tumor cells being a hallmark of primary glioblastomas. The giant cell glioblastoma occupies an intermediate position. Like the primary glioblastoma, it rapidly develops de novo but manifests in younger patients (including children) and has genetic alterations typical for secondary glioblastomas, i.e. frequent TP53 mutations and lack of EGFR overexpression.

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