

ONCOGENOMICS OF MENINGIOMA

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A loss of function of the *NF2* gene on chromosome 22q is thought to be an initiating event in the development of almost half of all meningiomas, and loss of chromosome 22q (which frequently accompanies *NF2* mutation) is one of the earliest and most frequent large scale chromosomal changes observed in these tumors. In addition to 22q loss, most meningiomas that display rapid growth or recurrence show additional large scale chromosomal abnormalities indicative of marked chromosomal instability. However, the factors contributing to the accumulation of these changes are not known. We have performed a genome-wide analysis of initial and recurrent pairs of meningiomas, and find that the accumulation of chromosomal alterations accompanies tumor progression.

Moreover, we have identified a gene defect (other than *NF2* mutation) that is present in a majority of clinically aggressive meningiomas and that correlates with defective DNA repair in meningioma cells. In laboratory studies, we find that this gene defect promotes chromosomal instability in meningioma cells. These findings suggest a new model of meningioma development in which *NF2* loss leads to tumor initiation, but other specific gene defects promote chromosomal instability and tumor progression.

Another major finding from our genome-wide analysis of meningioma is the discovery of a new tumor suppressor gene that is deleted in aggressive meningiomas and in many other cancers. The protein product of this gene appears to regulate cell growth and metabolism. Studies are currently underway to determine the molecular mechanisms by which loss of this gene promotes tumor growth.