Brain cancers
DNA chips improve diagnosis of gliomas

Institut Curie and Inserm research scientists and physicians have just shown that precise knowledge of alterations in chromosome 1 can be used to improve the treatment of gliomas, the most frequent brain tumors in adults. Diagnosis and treatment of these tumors are difficult because of their heterogeneity and variable malignancy. Using DNA chips, the authors of this report were able to distinguish the tumors with the best prognosis, whose chromosome 1 has undergone a specific deletion. Screening for these deletions should be incorporated into standard diagnostic tests by the end of 2005.

These results are published in the September 2005 issue of *Annals of Neurology*.

Gliomas are the most frequent brain tumors in adults, and account for over 50% of primary tumors. They are classified into three groups: astrocytomas – 70% of all these tumors – derive from astrocytes, cells close to the neurones; oligodendrogliaomas derive from cells that produce the sheaths of nerve fibers; and oligoastrocytomas which are mixed tumors combining the characteristics of the first two types.

Gliomas are graded I to IV according to their malignancy. Grade 1 tumors are clinically benign and can be treated surgically. Grade II, III and IV tumors are increasingly malignant and require additional treatments (chemotherapy and/or radiotherapy).

Classification and grading of gliomas are essentially based on subtle microscopic characteristics and are therefore problematic. There is no specific marker or genetic signature, and the present classification seems inadequate in predicting the outcome of each type of glioma.

**Chromosome 1 and the prognosis of gliomas**

By studying the specific genetic alterations of a subgroup of more chemosensitive gliomas, their classification can be refined: the loss of the short arm of chromosome 1 has thus been associated with a better prognosis and improved response to chemotherapy.

Jean-Yves Delattre and his team at the Pitié-Salpêtrière Hospital and Olivier Delattre and his team at the Institut Curie have identified several types of deletions of chromosome 1, only one of which is associated with gliomas with a good prognosis. These findings were recorded using array CGH analysis (see "Further information"), a technique that can establish high-resolution maps revealing genome anomalies (amplifications, deletions). Only the complete loss of the short arm of chromosome 1 combined with complete loss of the long arm of chromosome 19 signifies a good prognosis. Partial loss of the short arm of chromosome 1, on the other hand, characterizes more aggressive tumors. This retrospective study was done with samples from the tumor library of the Pitié-Salpêtrière Hospital using a technology developed at the Institut Curie.

In terms of fundamental research, these findings suggest that the genes involved in these two deletions, and hence associated with gliomas of good and poor prognosis, are different.
In clinical terms, the array CGH technique should improve the diagnosis of gliomas and hence their treatment. Screening for these chromosome 1 deletions should be incorporated into standard diagnostic tests by the end of 2005.

Genomics and notably DNA chips generate new information on the alterations underlying cancers. Using these tools, physicians can revamp and refine tumor classification to enable more individualized treatments.

**Further information**

**Institut Curie researchers are experts in use of comparative genomic hybridization**

Comparative genomic hybridization (CGH) allows global analysis of the genome. It is the ideal tool to identify genome regions that have been amplified or deleted – very frequent events in tumor cells. CGH combines the techniques of cytogenetics and DNA chips.

New CGH chips – array CGH – are made using targets from genome fragments of about 150 000 base pairs. With some 3 500 targets, these chips afford an overview of the whole genome.

In practical terms, tumor DNA and normal DNA labeled with fluorescent molecules of different colors (red and green for instance) are spread on the chip. These two types of DNA (probes) hybridize with the targets on the chip, resulting in the appearance of luminescent spots. The relation between the two types of fluorescence is analyzed using a dedicated software, which determines the relative quantity of each probe. When red predominates, there is an excess of tumor DNA: the region considered has been amplified. When green is preponderant, only normal DNA has bound: this region has been deleted from the tumor DNA. When the two colors are present in equal amount, the tumor DNA has neither gained nor lost this region and the probe appears yellow.

**Reference**

*Two types of chromosome 1p losses with opposite significance in gliomas.*

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The CGH chip used in this study was prepared in the framework of the Tumor Profiling Program of the Ligue Nationale Contre le Cancer.

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¹ The study of these chromosomal alterations is called cytogenetics. Over the last decade, cytogenetics has resulted in a finer tumor classification while shedding light on the mechanisms of cancerogenesis.