日本人の皮膚悪性黒色腫の遺伝子異常に関する研究

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Molecular genetic investigation of Japanese cutaneous melanoma

Research Project

Project/Area Number

09670868

Research Category

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Allocation Type

Single-year Grants

Section

一般

Research Field

Dermatology

Research Institution

KANAZAWA UNIVERSITY

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melanoma / p16 / tumor suppressor gene / metastasis / loss of heterozygosity / chromosome / microsatellites

Research Abstract

In a systematical analysis in 46 Japnese sporadic primary cutaneous melanomas, we detected loss of heterozygosity (LOH) of chromosome region 9p21 (where the p16 resides) in 11 (24%) tumors. Direct sequencing, however, revealed no somatic mutation of the p16 gene. Further sequencing analyses in

19 additional tumours with no evidence of LOH of 9p21 identified only one heterozygous C->T mutation at codon 81. De novo methylation of the promoter 5'CpG island of the p16 gene, which would lead to transcriptional silencing, was not demonstrated in any of these 12 tumours harboring 9p21 LOH or heterozygous p16 mutation by methylation-specific PCR assay. Nonetheless, complete loss of p16 protein, most likely due to homozygous deletion of the p16 gene, was observed in 6 (15%) out of 39 evaluable cases by immunohistochemical analyses on frozen sections. The results show that inactivation of p16 is not as frequent in primary melanoma as has been reported in cell lines, and warrant further search for another tumour suppressor on 9p21 which is likely to be more important in the initiation of melanoma. Simultaneous investigation examining corresponding metastases in 14 cases showed complete loss of p16 expression during matastatic progression in 4 cases, suggesting that inactivation of p16 plays an important role in progression (rather than initiation) of sporadic melanoma. This analysis also compared LOH of chromosome arms 6q, 9p, 9q, 10q, 11q and 18q, and provided clear evidence that in 3 cases clones of cells found in the sites of metastasis did not derive from the dominant subclone within the primary tumor, indicating that a linear model of melanoma progression is too simplistic, as there is likely to be considerable genetic heterogeneity at the earliest stages of tumourigenesis and that metastases from the same tumor may harbor different genetic change.

Research Products (6 results)

All Other

All Publications (6 results)

[Publications] Morita R, Fujimoto A, Hatta N, Takehara K, and Takata M: "Comparison of genetic profiles between primary melanomas and their metastases reveals genetic alterations and clonal evolution during progression"J Invest Dermatol. 111. 919-924 (1998)

[Publications] Fujimoto A, Morita R, Hatta N, Takehara K, Takata M: "p16^<INK4a> inactivation is not frequent in uncultured sporadic primary cutaneous melanoma"Oncogene. 18. 2527-2532 (1999)

[Publications] Takata M, Morita R, Takehara K: "Clonal heterogeneity in sporadic melanomas as revealed by loss-of-heterozygosity analysis"Int J Cancer. 85. 492-497 (2000)

[Publications] Morita R, Fujimoto A, Hatta N, Takehara K, and Takata M: "Comparison of genetic profiles between primary melanomas and their metastases reveals genetic alterations and clonal evolution during progression."J Invest Dermatol. 111(6). 919-924 (1998)

[Publications] Fujimoto A, Morita R, Hatta N, Takehara K, Takata M: "p16イイD1INK4aイエD1 inactivation is not frequent in uncultured sporadic primary cutaneous melanoma."Oncogene. 18. 2527-2532 (1999)

[Publications] Takata M, Morita R, Takehara K: "Clonal heterogeneity in sporadic melanomas as revealed by loss-of-heterozygosity analysis."Int J Cancer. 85. 492-497 (2000)

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