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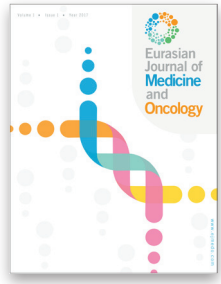

Review

Frequency of RAS Mutations (KRAS, NRAS, HRAS) in Human Solid Cancer

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Abstract

RAS oncogene affects numerous cellular functions including growth, proliferation, apoptosis, migration, division and differentiation of the cells. It has 3 known isoforms as Harvey- RAS (HRAS), Kirsten - RAS (KRAS) and Neuroblastoma-RAS (NRAS). RAS has an intrinsic GTPase activity. It encodes proteins binding the guanine nucleotides. KRAS and HRAS were discovered in studies carried out on viruses leading to cancer. Retroviral oncogenes related to murine sarcoma virus genes (Kristen Rat Sarcoma Virus and Murine Sarcoma Virus) were discovered in 1982. These two oncogenes are similar to human KRAS. Approximately 30% of all human cancers have ras genes. Mutations in KRAS account for about 85% for all RAS mutations in human tumors, NRAS is about 11–15%, and HRAS is about 1%.

Keywords: KRAS, NRAS, HRAS, cancer

The RAS oncogene affects numerous cellular functions, including growth, proliferation, apoptosis, migration, division, and differentiation of the cells. It has 3 known isoforms: Harvey-RAS (HRAS), Kirsten-RAS (KRAS), and neuroblastoma-RAS (NRAS). RAS has an intrinsic GTPase activity; it encodes proteins binding the guanine nucleotides. KRAS and HRAS were discovered in studies conducted on cancer-causing viruses. Retroviral oncogenes related to murine sarcoma virus genes (Kristen rat sarcoma virus and Harvey rat sarcoma virus) were discovered in 1982. These 2 oncogenes are similar to human KRAS. Approximately 30% of all human cancers have RAS gene involvement. Mutations in KRAS account for about 85% of all RAS mutations in human tumors, NRAS for about 11% to 15%, and HRAS for about 1%.[1–6]

Frequency of RAS mutation in intracranial tumors

Gliomas constitute 80% of malignant brain tumors. RAS mutations are very rare in malignant gliomas; no RAS mutation was found in a study in which 30 glioblastoma multiforme (GBM) patients were evaluated. The frequency of NRAS mutation was 2.1% in another study, although KRAS and HRAS mutations were not detected. It was reported that RAS mutation frequency was 12% in a study of isocitrate-dehydrogenase 1-mutant malignant glioma. RAS genes were studied in 21 cases of glioblastoma multiforme, 4 cases of fibrillary astrocytoma, 4 cases of anaplastic astrocytoma, and 15 normal specimens. RAS mutation was de-

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tected in 1 normal and 1 pathological sample. It was concluded that brain tumor development was found to involve KRAS and HRAS mutations, while NRAS mutation may play a lesser role. The frequency of RAS mutation in GBM is 2% in the atlas of the human genome. KRAS mutation was found in 4.7% of pilocytic astrocytomas, while there was no NRAS and HRAS mutation. RAS mutations in oligodendrogliomas have not yet been sufficiently researched.[7–15]

Frequency of RAS mutation in head and neck cancers

Many head and neck cancers are squamous cell carcinomas. More than half a million people are affected every year. The prevalence has continued to gradually increase in recent years.[16] Overall survival in patients with KRAS mutation head and neck tumor is worse. KRAS mutations also demonstrate social differences in head and neck tumors, like many cancers. Though the mutation frequency is 5% in oral cavity tumors in Western societies, it can be seen in up to 18% of cases in Eastern societies. The frequency of KRAS mutation in malignant larynx lesions was 4.8% in one study performed, while there were no HRAS and NRAS mutations. In Eastern societies, the frequency of HRAS mutation in oral cavity tumors can be as much as 35%. KRAS mutation was not detected at all in mouth and hypopharynx cancers in another study conducted. There is KRAS mutation in 11.5% and 3.3% of patients with laryngeal cancer and oropharynx cancer, respectively. NRAS mutation in nasopharynx cancer is reported as 4%, while HRAS mutation is <1% and KRAS mutation is very rare.[17–21]

Frequency of RAS mutation in gastrointestinal cancer

Colorectal cancers are one of the leading causes of cancer-related death, though incidence and mortality have decreased in recent years. This is probably due to early diagnosis and screening methods. RAS mutation testing is frequently used in everyday practice in cases of metastatic colorectal cancer. RAS mutations are significant in the selection of targeted treatment. There is no marker for the use of bevacizumab; however, KRAS wild tumors are a marker for the use of cetuximab, and KRAS and NRAS wild colorectal tumors are a marker for the use of panitumumab. The frequency of KRAS mutations in colorectal cancers varies from 27% to 56% from community to community. The frequency of NRAS mutations in colorectal cancers is between 1% and 7%. NRAS mutation frequency is 5.3%, 4.1%, and 2.2% in Romanian, Italian, and Chinese patients, respectively. There is almost no HRAS mutation seen in colorectal cancers. KRAS mutations do not seem to be prognostic in colorectal

Table 1. Frequency of RAS mutations according to cancer type

Cancer	KRAS %	NRAS %	HRAS %
Glioblastoma multiforme	0–2	2.1	0
Pilocytic astrocytoma	4.7	0	0
Oligodendroglioma	LD	LD	LD
Oral cavity tumor	0–18	<1	35
Larynx cancer	4.8–11.5	0	0
Nasopharynx cancer	0	4	<1
Colorectal cancer	27–56	1–7	<1
Stomach cancer	2.8–9.4	1.9	<1
Pancreatic cancer	90	<1	<1
Hepatocellular cancer	0–5	15	29
Cholangiocarcinoma	16–38	LD	<1
Small cell lung cancer	1–16	<1	<1
Squamous cell lung cancer	3	<1	<1
Lung adenocarcinoma	12–36	<1	<1
Large cell lung cancer	14	<1	<1
Large cell lung cancer	<1	<1	<1
Serous ovarian carcinoma	6	8	<1
Ovarian clear cell carcinoma	14	0	
IMSC	68		
Low-grade serous tumour	29.5		
High-grade serous carcinoma	12		
Mucinous borderline tumor	33–78		
Serous borderline tumor	60		
Mucinous carcinoma	46–75		
LGOEC	33		
Endometrial cancer	11–35		
LGEEC	18		
NEEC	0–5		
Cervical cancer	5–14	<1	<1
Cervical squamous cell carcinoma	<1		
Cervical adenocarcinoma	10		
Prostate adenocarcinoma	7–9		
Vulvar cancer	1		9
Germ cell testicular tumor	6	6	LD
Seminoma	6–18	<1	LD
Non-seminoma	0–9	<1	LD
Bladder cancer	0–4	0–80	0–84
Renal cell carcinoma	0–16	<1	<1
Clear cell renal cell carcinoma	0–100	<1	<1
Soft tissue sarcoma	0–44	<1	0–16
Cutaneous malignant melanoma	<1	15–30	<1
Breast cancer	7–12	5	<1
Luminal A	2		
Luminal B	20		
HER2 overexpression	17		
Triple negative	0–8		

KRAS: Kirsten - RAS; NRAS: Neuroblastoma- RAS; HRAS: Harvey- RAS: IMSC: Invasive micropapillary serous carcinoma; LGOEC: Low-grade ovarian endometrioid carcinomas; LGEEC: Low-grade endometrial endometrioid carcinoma; NEEC: Non- endometrioid endometrial cancer; LD: Limited data

cancers, but are predictive. NRAS mutations also show geographical and ethnic differences in colorectal cancers, like KRAS mutations. The frequency of KRAS mutations in the right and left colon is different. Exposure to embryogenesis and/or carcinogens may play a role in this difference. The left colon is subject to carbonaceous substances for a greater period of time. It is interesting that there are fewer KRAS mutations in the left colon than in the right colon. The first column shadow subject to carcinogenic substances is the right colon. The right colon may be more sensitive to carcinogenic substances.

Stomach cancers are observed more often in Third World countries and Eastern societies. KRAS mutation frequency in gastric cancer has ranged from 2.8% to 9.4% in studies. NRAS mutation in gastric cancer can be found in 1.9%. HRAS mutation is very rare in gastric cancer. KRAS mutation is present in over 90% of pancreatic cancers. There are almost no NRAS and HRAS mutations in pancreatic cancers. KRAS mutation in hepatocellular cancer is 0% to 5%, while NRAS mutation is 15%. HRAS expression in hepatocellular cancer is 29%. KRAS mutation prevalence in cholangiocarcinoma ranged from 16% to 38%.[22–36]

Frequency of RAS mutation in lung cancer

Lung cancer is one of the most deadly cancers and is closely associated with tobacco use. Recent RAS mutation studies have most often focused on lung cancers. The incidence of KRAS mutation in small cell lung cancer (SCLC) is between 1% and 16%. SCLC has a close relationship with tobacco use; KRAS mutation is low in SCLC. KRAS mutation frequency in squamous cell lung carcinoma associated with tobacco use is 2.7%. The frequency of KRAS mutation in lung adenocarcinomas is between 12% and 36%. KRAS mutation in never-smoker lung adenocarcinoma patients is 15%, while it is 22% in former smokers and 25% in current smokers. KRAS mutation is common in smoking lung adenocarcinoma patients. Interestingly, KRAS mutation is observed to be less common in SCLC and squamous cell lung cancer, which are closely associated with tobacco usage. KRAS mutation in large cell lung cancer is 14%. The effect of KRAS mutation on prognosis in lung adenocarcinoma is controversial. KRAS mutation in SCLC is not prognostic. NRAS mutation frequency is 1% in non-small cell lung cancer (NSCLC). NRAS mutations are more frequent in NSCLC patients who smoke. KRAS mutation is 0% while NRAS mutation is 20% in neuroendocrine lung cancer. HRAS mutations are observed very rarely in lung cancers (<1%). There is almost no KRAS mutation in malignant mesothelioma.

Genetic, dietary, and environmental factors seem to play a role in the development of KRAS mutation.[6, 37–45]

Frequency of RAS mutation in genitourinary cancer

RAS mutation frequency in cancer overall is 27%. Ovarian clear cell carcinoma constitutes 15% of all ovarian cancers. KRAS mutation frequency is 14% in ovarian clear cell carcinoma, and there is no NRAS mutation. The frequency of NRAS mutation in epithelial ovarian cancer is 8%. KRAS mutation prevalence is 68%, 29.5%, 12%, 33%–78%, 60%, 46%–75%, 6%, and 33% in invasive micropapillary serous carcinoma, low-grade serous tumor, high-grade serous carcinoma, mucinous borderline tumor, serous borderline tumor, mucinous carcinoma, serous ovarian carcinoma, and low-grade ovarian endometrioid carcinoma, respectively. In ovarian cancer, the frequency of KRAS mutation varies greatly according to the histological subtype. The data regarding KRAS mutation are limited. The frequency of KRAS mutation in endometrial cancer ranges from 11% to 35%. Lymph node metastasis is more common in KRAS mutation endometrial cancer patients. KRAS mutation in low-grade endometrioid endometrial carcinoma is 18%. KRAS mutation is 0% to 5% in non-endometrioid endometrial cancers.[46–56]

The frequency of KRAS mutations in cervical cancer ranges between 5% and 14%. In the United States, the frequency of KRAS mutation is 8.8% in patients with cervical cancer. KRAS mutation is 10% in patients with cervical adenocarcinoma. KRAS mutation is very rare in cervical squamous cell carcinomas. There is no relationship between KRAS mutation and survival in cervical cancer. The KRAS mutation prevalence is 5.3% in Chinese cervical cancer patients. This rate is 13.7% in young Chinese cervix cancer patients. KRAS mutation is more frequent in non-squamous cervical cancer than squamous cervical cancer. NRAS mutation prevalence is <1%, while HRAS mutation prevalence is <0.5% in cervical cancers. KRAS mutation is present in 7% to 9% of prostate adenocarcinomas. In vulvar cancer, HRAS mutation is 9% and KRAS mutation is <1%, and survival is worse in patients with RAS mutation. The prevalence of KRAS and NRAS mutations in germ cell testicular tumors is approximately 6%. The frequency of KRAS mutation in seminoma varies from 6% to 18%. KRAS mutation frequency is 0% to 9% in non-seminoma germ cell tumors and NRAS mutation is rare. KRAS mutation in bladder cancer is 0% to 4%. NRAS mutation in bladder cancer is 0% to 80%, and HRAS mutation is 0% to 84%. The frequency of HRAS and NRAS mutations in bladder cancer ranges from 0% to 84%, with very different results in studies conducted. The frequency of mutation in urethral carcinoma is 4% to 29%. The frequency of KRAS mutation in renal cell carcinoma was determined to be 0% to 16%. Although KRAS mutation fre-

quency is 0% to 1% in many studies of clear cell renal cell carcinoma (RCC), it has also been reported in some studies that the frequency of KRAS mutation was 100%. NRAS and HRAS mutations are very rare in renal cell carcinoma. KRAS and NRAS mutations are <3% in adrenocortical cancer.[57–80]

Frequency of RAS mutation in skin and soft tissue sarcoma

HRAS mutation and KRAS mutation were identified with a prevalence of 0% to 16% and 0% to 44%, respectively, in studies of soft tissue sarcoma. NRAS mutation is rare in soft tissue sarcoma. NRAS mutation is found in approximately 15% to 30% of cutaneous malignant melanoma cases. KRAS and HRAS mutations are rare.[6, 81–85]

Frequency of RAS mutation in breast cancer

Breast cancer is the most common cancer in women. The prevalence of RAS mutation in breast cancer is between 7% and 12%. In a study in which patients receiving neoadjuvant cyclophosphamide and doxorubicin chemotherapy were evaluated, KRAS mutation was found in 2% of luminal A tumors, 20% of luminal B, 17.4% of HER2 overexpression, and 7.7% of triple negative tumors. There are also studies in which KRAS mutation was not detected in triple negative breast cancer. KRAS mutation has critical importance in the ability to develop metastases of basal-like tumors. KRAS mutation breast cancers are associated with worse prognosis. NRAS mutation in breast cancer can be found in 5% of cases Table 1.[86–88]

Conclusion

RAS mutation prevalence varies in cancer. RAS mutations provide preliminary information for cancer aggressiveness. RAS mutations also display social differences in the same type of cancer. Genetic and environmental factors seem to have a role in development of RAS mutations. The frequency of RAS mutations in cancer will probably increase with the increase in the number of known mutations. KRAS mutations are predictive in colorectal cancer. Although KRAS mutations are more frequent in lung adenocarcinoma patients who are smokers, it is interesting to observe it less in small cell lung cancer. Frequency of KRAS mutation differs according to the embryonic development area of the colon in colorectal cancer. It seems that KRAS mutations will have a more important role in the coming years, in addition to being an indicator in the choice of targeted treatment.

Disclosures
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