Journal of Medical Genetics and Genomics Vol. 3(9), pp. 140 - 144, December 2011
Available online http://www.academicjournals.org/jmgg
DOI: 10.5897/JMGG11.017
ISSN 2141-2278 ©2011 Academic Journals

Full Length Research Paper

Relationship between *H-RAS* oncogene and uterine cancer

Majeed Hussein Al-Sarry

Nursing college, Basrah University, Iraq. E-mail: majeedalsary@yahoo.com.

Accepted 20 October, 2011

The current study is skillful to detect the mutations of the *H-RAS* oncogene in patient of uterine cancer. Thirty specimens of blood and tissue were collected for DNA extraction, *H-RAS* oncogene amplification and histopathology examination. The results, which revealed presence of mutations in *H-RAS* oncogene represented by homozygous wild type Leu/Leu was 20%, mutant translocation genotype Val/Val was 48%, mutant deletion genotype Val/Leu was 22% and heterozygous genotype Leu /Val was 10%. The histopathological results of this study reveal too many types of uterine cancer. The major types of uterine cancer that appear in this study represented by endometrial adenosquamous carcinoma are associated with endometrial lieomyosarcoma, the other cases were represented as endometrial spheriodal cell carcinoma and as endometrial intra epithelial carcinoma.

Key words: *H-RAS* gene, uterine cancer, DNA.

INTRODUCTION

Uterine cancer begins when normal cells in the uterus change and grows uncontrollably, forming a mass called a tumor. There are two major types of uterine cancer, adenocarcinoma, and this type of cancer makes up more than 95% of uterine cancers; it develops from cells in the lining of the endometrium. This cancer is also commonly called endometrial cancer. Sarcoma is the second form of uterine cancer that develops in the myometrium or in the supporting tissues of the uterine glands (Cancer_Net .mht, 2011). It has been reported that the ras gene family (*K-RAS, H-RAS,* and *N-RAS*) is associated with the development of human neoplasms (Barbacid, 1987). Single-point mutations of the ras gene, usually at codons 12, 13, and 61, result in a single amino acid substitution in critical domains, and this substitution has a significant role in tumor development by making the proteins no longer dependent on GTPase (guanosine5'-triphosphatase)-activating protein regulation. Frequent ras mutations have been reported in a number of human cancers, including adenocarcinoma of the pancreas (90%), colon (50%), thyroid (50%), and lung (30%) (Bos, 1989). The *H-RAS* gene commonly is activated in human urinary tract tumors. H-RAS mutations have been reported in malignant fibrous histiocytoma (MFH), leiomyosarcoma, and rhabdomyosarcoma as for sarcomas (Wilke et al., 1993; Bohle et al., 1996; Yoo and Robinson, 1999; Yoo et al., 1999).

MATERIALS AND METHODS

A total of thirty patients women with uterine cancer were contacted after surgery. The blood samples were collected in sterilized tube with EDTA, brought to the laboratory and kept directly in -20°C till used for DNA extraction, while the tissue samples were collected from endometrial cancer for histopathological study and kept in formalin 10% for 48 h (Luna,1968). Genomic DNA was isolated by DNA extraction kit. The mutation of the codon 12 of *H-ras* oncogene was studied according to protocol of Chikako et al. (1994). Briefly genomic DNA was amplified using the primers Forward5´- CTCTATAGTGGG ATCATAC-3´, Reverse5´-GACTCCTACCGGA AAC AGG-3´. PCR reaction mix and condition are PCR green master mix 12.5 µl, Primer forward 1 µl, Primer reverse1 µl, DNA 5 µl, D.W. 5.5 and 25 µl mineral oil. PCR conditions were denaturation 94°C for 5 min 1 cycle, denaturation 94°C for 1 min annealing 58°C for 1.5 min, extension 72°C for 2.5 min. and 30 cycles and extension 72°C for 5 min 1 cycle. The PCR product was 108 pb, and then subjected to electrophoresis on a 2% agarose gel. PCR product was digested for 3 h at 37°C with *Eco R1* restriction enzyme using 3 µl of NE buffer 2, 0.5 µl (5 units) of enzyme and 10µl of PCR product, 0.3 µl BSA. The PCR products were classified as homozygous wild type (80 to 28 bp), translocation mutant genotype (108 bp), heterozygous (108-80 bp) alleles, deletion mutant genotype (80 bp).

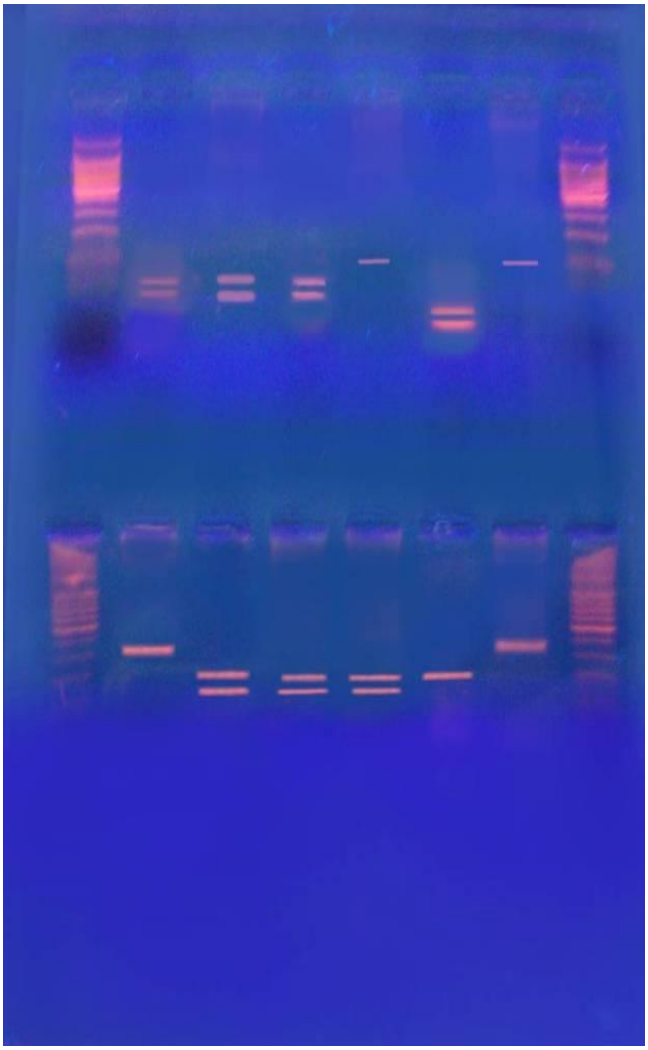

Figure 1. PCR analysis of the codon 12 of *H-RAS* oncogene using *Eco R1* restriction enzyme. lane 1, 8,9,16 ladder, lane14 mutant deletion genotype, lane 5,7,10 and 15 mutant translocation genotype, lane 6,11,12 and 13 homozygous wild type , lane 2,3&4 heterozygous genotype.

RESULTS AND DISCUSSION

The results showed the mutations of the *H-RAS* oncogene (Figure 1). The frequency of patient with uterine cancer *H-RAS* oncogene homozygous wild type Leu/Leu was 20%, while that of mutant translocation genotype Val/Val was 48%. The mutant deletion genotype Val/Leu was 22%. The heterozygous genotype Leu/Val was 10%. The histopathological results of the current study revealed too many types of uterine cancer (Table 1). Twenty six cases from the total were represented by endometrial adenosquamous carcinoma associated with 16 cases endometrial lieomyosarcoma (Figures 2, 3, 5, 6 and 9), three cases were represented as endometrial spheriodal cell carcinoma (Figures 4 and 7). One case appears as endometrial intra epithelial carcinoma (Figure 8)

GTPase *H-RAS* is involved in regulating cell division in response to growth factor stimulation. Growth factors act by binding cell surface receptors that span the cell's plasma membrane. Once activated, receptor stimulate signal transduction events in the cytoplasm, a process by which proteins and second messengers relay signals from outside the cell to the cell nucleus and instructs the cell to grow or divide. The *H-RAS* protein is a GTPase and is an early player in many signal transduction pathways and is usually associated with cell membranes due to the presence of an isoprenyl group on its C-terminus. Somatic mutations in the *H-RAS* gene are probably involved in the development of several other types of cancer. These mutations lead to an *H-RAS* protein that is always active and can direct cells to grow and divide without control. Recent studies suggest that *H-RAS* mutations may be common in thyroid and kidney cancers. The *H-RAS* protein also may be produced at higher levels in other types of cancer cells (Wong et al., 1981; Russell et al., 1996). Since *RAS* communicates signals from outside the cell to the nucleus, mutations in *RAS* genes can permanently activate it and cause inappropriate transmission inside the cell, even in the absence of extracellular signals. Because these signals result in cell growth and division, dysregulated *RAS* signaling can ultimately lead to oncogenesis and cancer (Goodsell, 1999). Activating mutations in *RAS* are found in 20 to 25% of all human tumors and up to 90% in specific tumor types (Downward, 2003). The cells become cancer cells because of the damage to the DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged, the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell does not die. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does. People can inherit damaged DNA, but most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking; but often no clear cause is found (American Cancer Society, 2011). The present study showed the significant increase in accidences of uterine cancer in Iraq women may be due to the exposure to war weapons pollutant during war. Also the bioaccumulation of pollutants from the environment to water and diet such as oil ship leak, sewages drains, pesticides, herbicides, and the use of poisonous chemicals may increase the incidence of endometrial cancer (Al-Kurishy, 2008).

CONCLUSIONS AND RECOMMENDATIONS

Increased risk of uterine cancer incidence in women who had mutant translocation genotype deletion and heterozygous genotype of *H-RAS* oncogene, as most of

Table 1. Show the type and percentage of uterine cancer.

Type of uterine cancer	Number of cases 30	Percentage (%)
Endometrial adenosquamous carcinoma with Endometrial lieomyosarcoma (16)	26	86.667
Endometrial spheriodal cell carcinoma	3	10
Endometrial intra epithelial carcinoma	1	3.333

* 16 cases of endometrial lieomyosarcoma associated with the 26 cases of endometrial adenosquamous carcinoma.

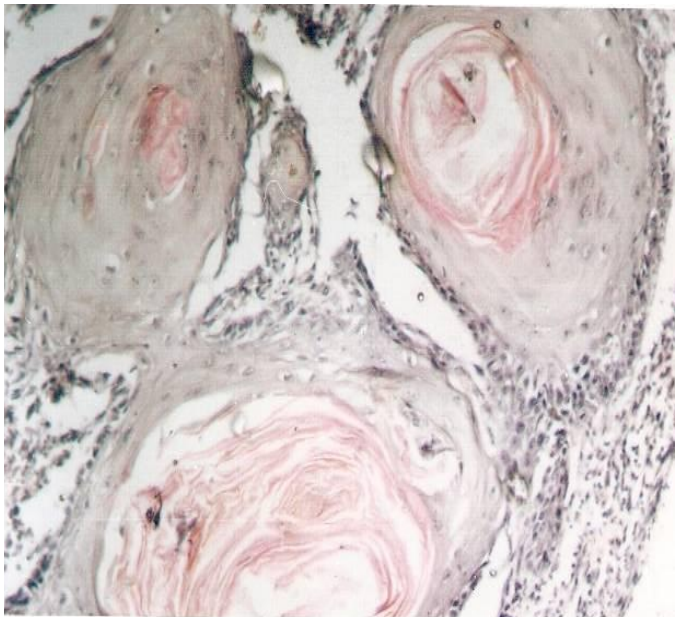

Figure 2. (H and E 250X).

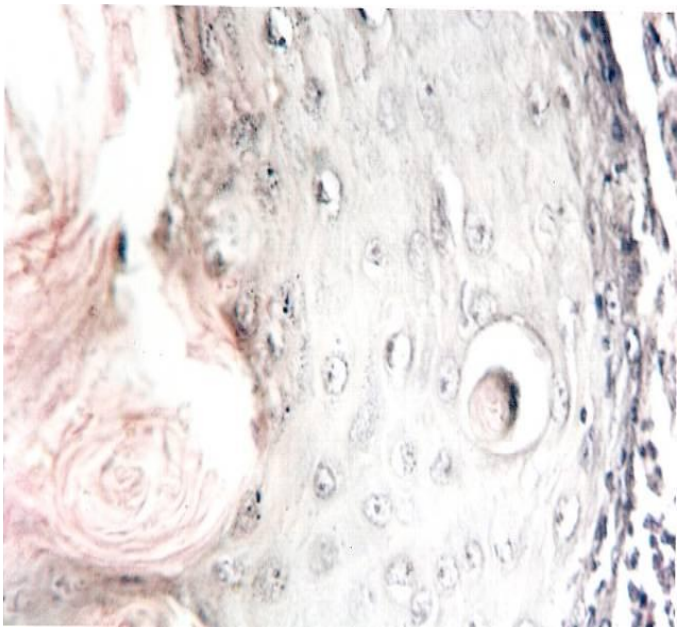

Figure 3. (H and E 250X).

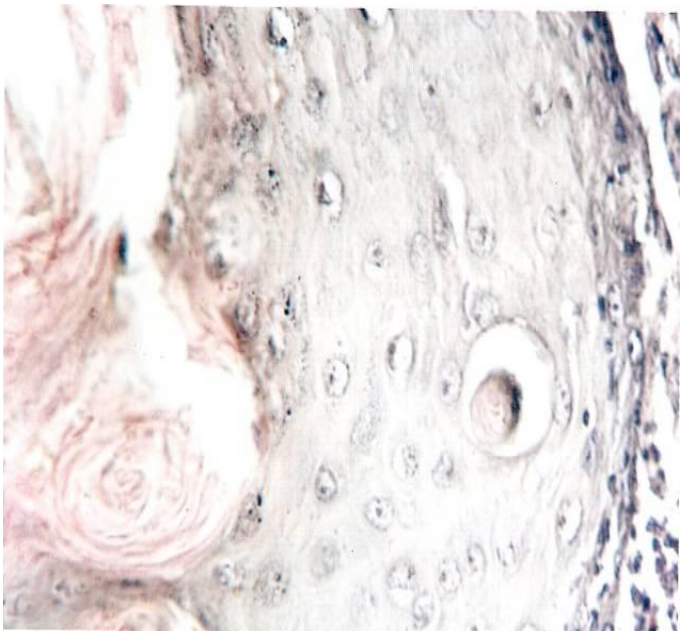

Figure 3. (H and E 250X).

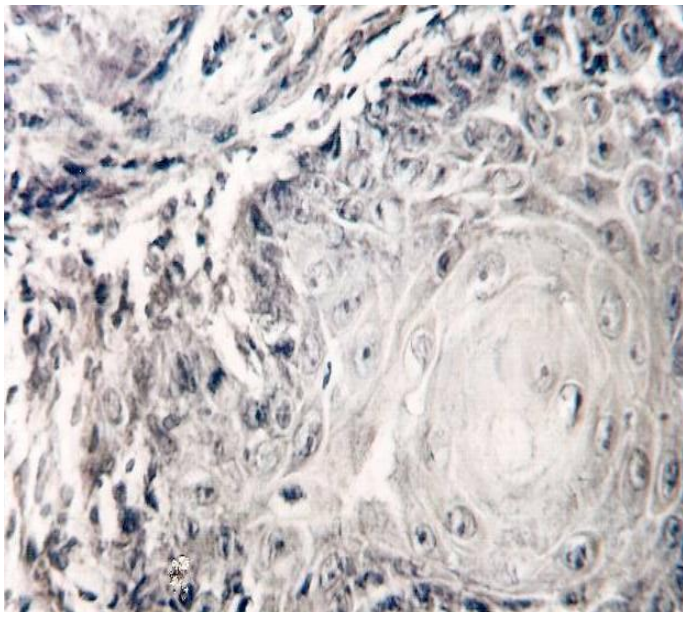

Figure 5. (H and E280X).

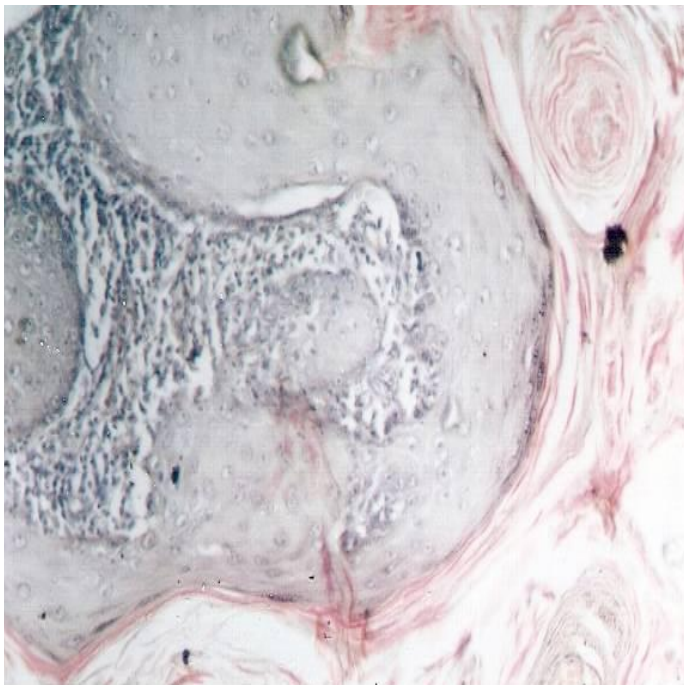

Figure 6. (H and E200X).

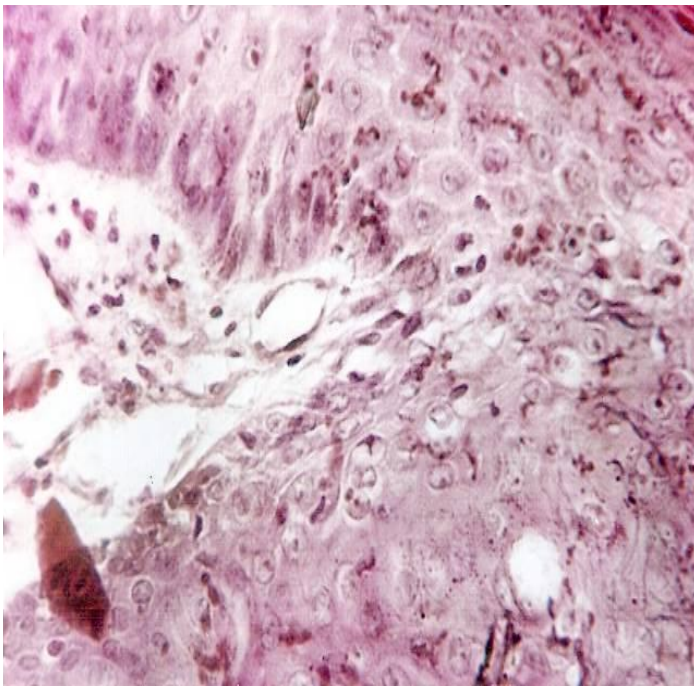

Figure 8. (H and E280X).

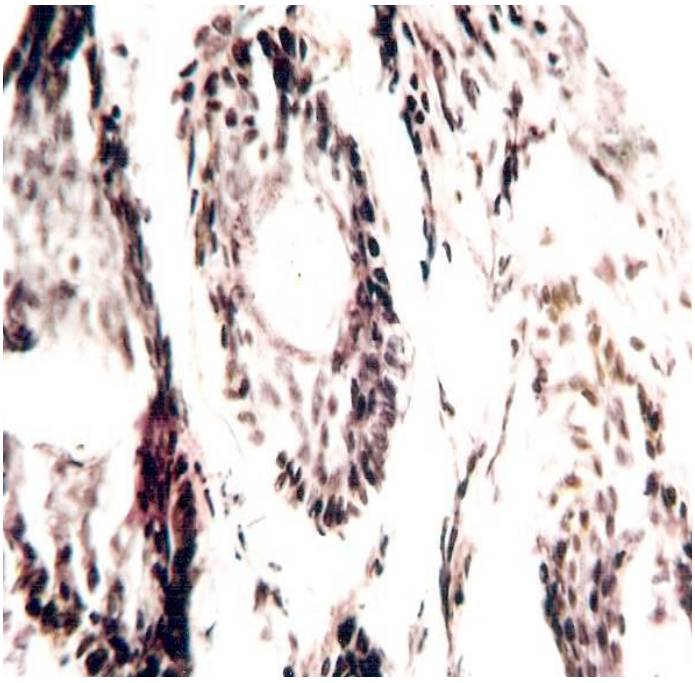

Figure 7. (H and E250X).

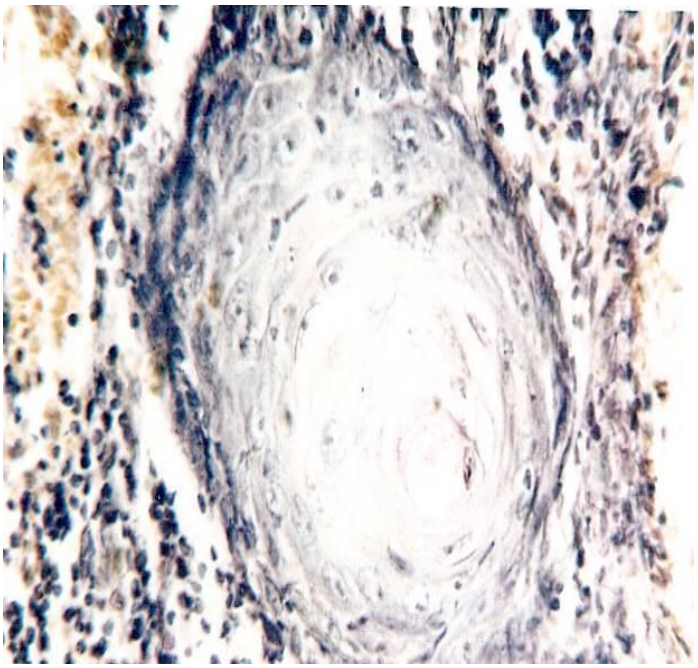

Figure 9. (H and E250X).

the cases, were endometrial adenocarcinomas with lieomyosarcoma. This study recommended that women should be less exposed to radiation, chemical hazardous substances and treatment with hormones to reduce mutation. Further studies are required to determine the relationship between endometrial cancer and other related genes.

ACKNOWLEDGMENTS

After praising God, the author gratefully acknowledge Dr. Khitam Jassim Salih for providing patient uterine cancer tissues and blood specimens used in this study.

REFERENCES

American Cancer Society (2011). Last Medical Review: 3/28/2011Last Revised:6/21/2011 www.cacer.org.

AL-Kurishy KJ (2008). The role of CYP1P1 and COMT genes polymorphism as a risk factors of Endometrial cancer in women . A thesis for Doctor of philosophy in bio– technology . collage of science . Basrah University

Barbacid M (1987). ras genes. Annu Rev Biochem.;56: 779-827

Bohle RM, Brettreich S, Repp R, et.al. (1996). Single somatic ras gene point mutation in soft tissue malignant fibroushistiocytomas. Am J Pathol.;148:731-738.

Bos JL (1989). Ras oncogenes in human cancer: a review. Cancer Res.;49:4682-4689)

Chikako N, Suming W, Junji M, Mayumi S, Toshihiko T, Takashi Y, Sadao I, Hiraku T (1994). Mutations in *ras* genes in cells cultured from mouse skin tumors induced by ultraviolet irradiation. Proc. Natl. Acad. USA, 91: 7189-7193. www. Oncologist-approved cancer information from the American Society of Clinical Oncology Cancer_Net.mht,2011

Downward J (2003). Targeting RAS signalling pathways in cancer therapy. Nat. Rev. Cancer, 3(1): 11-22.

Goodsell DS (1999). The molecular perspective: the ras oncogene. Oncologist, 4(3): 263-264. PMID 10394594. http://theoncologist.alphamedpress.org/cgi/content.

Luna LG (1968). Manual of histology stain methods of armed force institute pathology. 3rd Ed. The Blackstone diction. McGraw Hill book Company. New York, London and Sydney.

Russell MW, Munroe DJ, Bric E, Housman DE, Dietz-Band J, Riethman HC, Collins FS, Brody LC (1996). A 500-kb physical map and contig from the Harvey ras-1 gene to the 11p telomere". Genomics, 35(2): 353-360. doi:10.1006/geno.1996.0367. PMID 8661149.

Wilke W, Maillet M, Robinson R (1993). H-ras-1 point mutations insoft tissue sarcomas. Mod. Pathol., 6: 129-132.5

Wong-Staal F, Dalla-Favera R, Franchini G, Gelmann EP, Gallo RC (1981). Three distinct genes in human DNA related to the transforming genes of mammalian sarcoma retroviruses". *Science* 213 (4504): 226-228. doi:10.1126/science.6264598. PMID 6264598.

Yoo J, Robinson RA, Lee JY (1999). H-ras and K-ras gene mutationsin primary human soft tissue sarcoma: concomitant mutations of the ras genes. Mod. Pathol., 12: 775-780.)

Yoo J, Robinson RA (1999). H-ras and K-ras mutations in soft tissuesarcoma: comparative studies of sarcomas from Korean andAmerican patients. Cancer, 86: 58-63.