

Gene Section

Review

HMGA2 (high mobility group AT-hook 2)

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Abstract

HMGA2, the High Mobility Group A2 gene, is a non-histone and architectural transcription factor. As an oncofetal protein, HMGA2 plays an important role in development and contributes to the tumorigenesis of many epithelial and mesenchymal tumors.

Upregulation of HMGA2 by non-random chromosomal translocations is common in mesenchymal tumors, whereas by the altered transcription regulation is likely the major mechanism in malignant epithelial tumors and it involves much more complex mechanisms. HMGA2 directly and indirectly regulates the multiple biological and oncogenic pathways. Its oncogenic property remains to be fully characterized.

Keywords

HMGA2, Development, miRNA regulation, Stem cell self-renewal, transcription regulation, Oncofetal protein, neoplasia, Aging and senescence, epithelial-to-mesenchymal transition (EMT), non-random chromosomal translocation.

Identity

Other names: HMGIC, BABL, LIPO, STQTL9

HGNC (Hugo): HMGA2

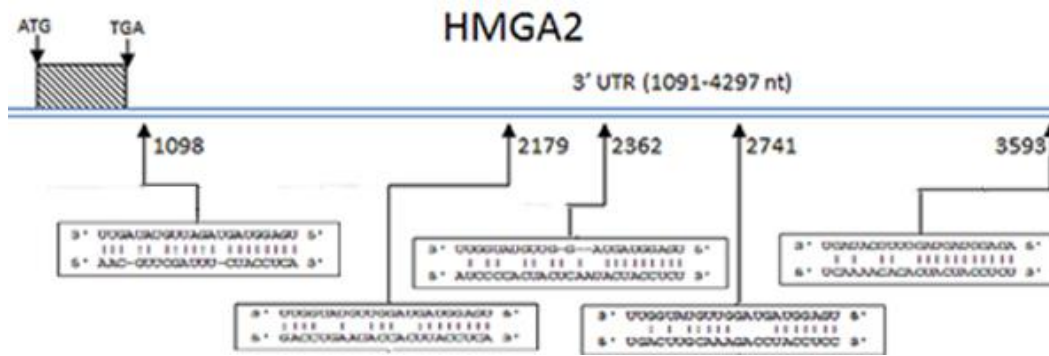
Location: 12q14.3

Local order

telomeric to CDK4, centromeric to MDM2



FISH Probe(s) - Courtesy Mariano Rocchi



HMGA2 has long UTR (about 3,000 nt). HMGA2 can be potentially regulated by multiple miRNAs and one of well characterized miRNAs is let-7 family which contains at least five predicted bindings sites. MIRLET7E (Let-7) repression of HMGA2 expression at transcription and translation has been demonstrated in several different studies (Lee and Dutta 2007, Wang et al. 2007, Peng et al. 2008). Inverse association of Let-7 and HMGA2 is an important regulation mechanism in normal development and abnormal tumorigenesis (Park et al. 2007, Shell et al. 2007).

DNA/RNA

Description

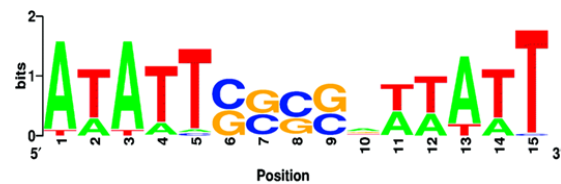
5 exons, spans approximately 160 kb; a sixth alternative terminal exon within intron 3 has been described

Transcription

RNA: 4.1 kb.

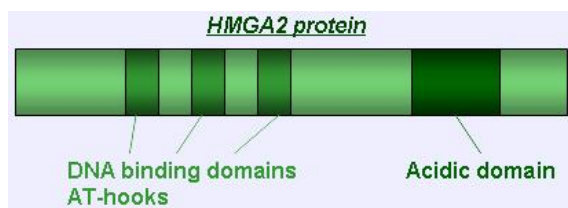
Transcription initiated from two different promoter regions. A polymorphic dinucleotide repeat upstream of the ATG start codon strongly regulates HMGA2 expression. Moreover, HMGA2 is controlled by negatively acting regulatory elements within the 3'UTR

hooks) linked to the carboxy-terminal acidic domain that does not activate transcription.



HMGA2 can directly regulate expression of many genes. Specific recognition of AT-rich DNA sequences by HMGA2 was reported by a SELEX study. The relative heights are proportional to their frequencies shown in the 71 SELEX sequences (Cui and Leng 2007).

Protein



Description

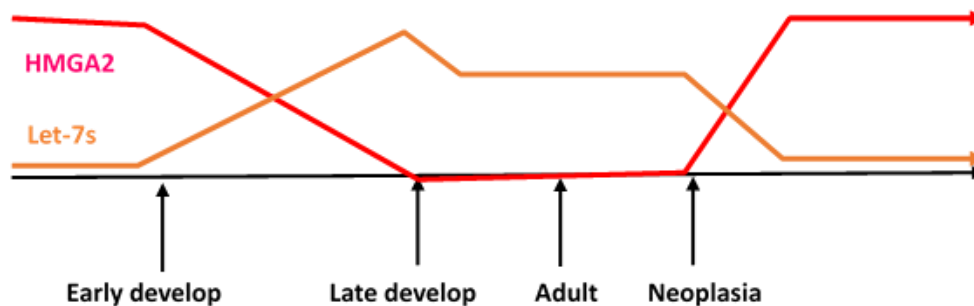
109 amino acids; three DNA binding domains (AT

Expression

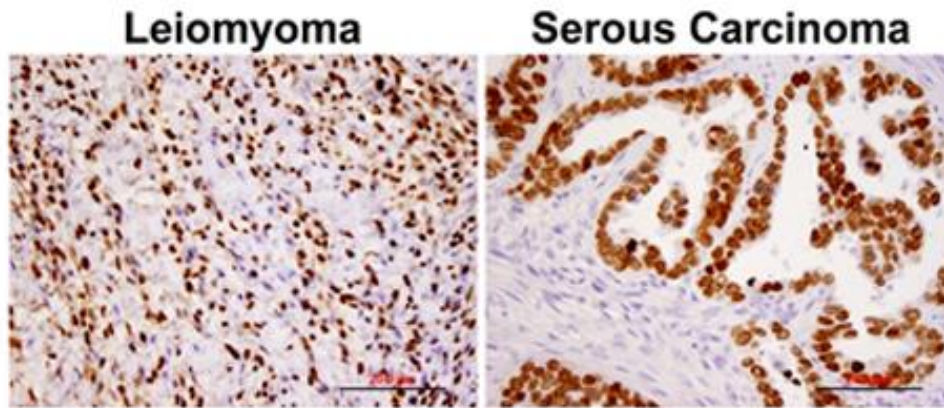
Fetal tissues: expression in various tissues, prominent in kidney, liver and uterus; **adult tissues:** no expression except in lung and kidney; **tumors:** expression in benign mesenchymal tumor tissues correlated to 12q15 rearrangements; expressed in malignant tumours (e.g., in breast tumours, pancreas tumours, ovarian cancer, lung tumours, colorectal cancer, nerve system tumours, oral cavity squamous cell cancer).

Localisation

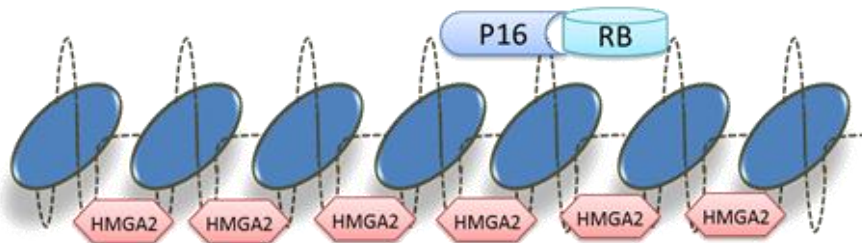
Nuclear



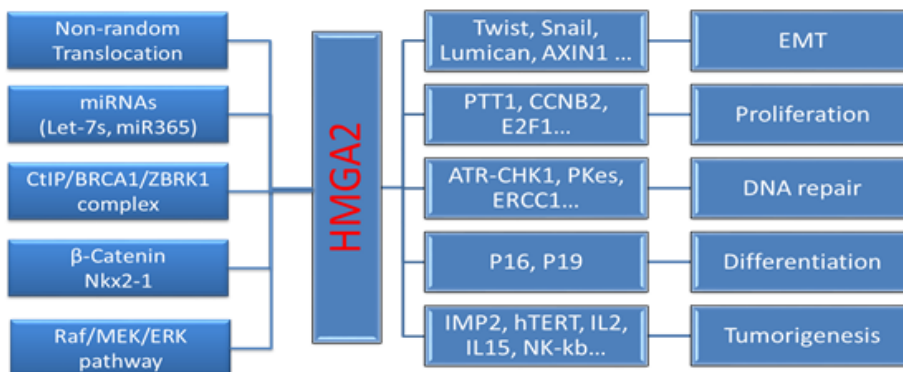
Inverse expression pattern of HMGA2 and let-7 family in developmental and adulthood stages as well as neoplastic change (Park, Shell et al. 2007).



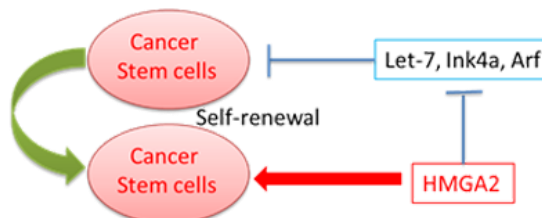
Immunohistochemistry shows that HMGA2 is specifically expressed and located in nucleus. Photomicrographs illustrate strong immunoreactivity for HMGA2 in leiomyoma with t(12;14) translocation and high grade serous ovarian carcinoma (Wu and Wei 2013, Bertsch et al. 2014).



It is widely accepted that functional CDKN2A (p16INK4a) and RB1 (pRb) as well as the HMGA2, which accumulate at E2F target promoters during senescence, are critically required for SAHF arrangement (Narita et al. 2006).



HMGA2 is regulated by non-coding miRNAs and coding genes. As a non-histone nuclear transcription regulator, HMGA2 has a broad influence in many gene expression, mainly target at epithelial-to-mesenchymal transition (EMT), cell proliferation, DNA damage repair, stem cell self-renewal and differentiation, as well as tumorigenesis of many benign and malignant mesenchymal and epithelial tumors (Wu and Wei 2013).



HMGA2 regulates stem cell potential for self-renewal. HMGA2 seems to be a major regulator of INK4a/ARF expression. HMGA2 reduces INK4A and ARF expression. HMGA2 binds to the Junb locus. As JUNB promotes INK4A/ARF expression in stem cells, thus promoting stem cell self-renewal. Increase in let-7 expression results in the downregulation of HMGA2 and the derepression of the INK4a/ARF and activation of p16INK4a expression in self-renewing cells. In Hmga2-deficient mice, it shows reduced stem cell numbers and self-renewal. Furthermore, p16(Ink4a) and p19(Arf) expression were increased in Hmga2-deficient fetal and young-adult stem cells, and deletion of p16(Ink4a) and/or p19(Arf) partially restored self-renewal capacity. (Yu et al. 2007, Nishino et al. 2008).

Function

Architectural factor, non histone, preferential binding to AT rich sequences in the minor groove of DNA helix; the precise function remains to be elucidated; probable role in regulation of cell proliferation.

Homology

Member of the HMGI protein family.

Mutations

Germinal

Deletion of HMGIC in mutant mice or transgenic 'knock out' mice for the first two exons of HMGIC have the "pigmy" phenotype: low birth weight, craniofacial defects, adipocyte hypoplasia adult body weight about 40% of normal; mice with a partial or complete deficiency of HMGA2 resisted diet-induced obesity implicating a role of the gene in fat cell proliferation; truncations of mouse *Hmga2* in transgenic mice result in somatic overgrowth and, in particular, increased abundance of fat and lipomas; overexpression of the HMGA2 gene in transgenic mice leads to the onset of pituitary adenomas secreting prolactin and growth hormone; HMGA2-null mice had very few spermatids and complete absence of spermatozoa.

8-year-old boy had a de novo pericentric inversion of chromosome 12, with breakpoints at p11.22 and q14.3.

The phenotype included extreme somatic overgrowth, advanced endochondral bone and dental ages, a cerebellar tumour, and multiple lipomas. His chromosomal inversion was found to truncate HMGA2, which maps to the 12q14.3 breakpoint.

Implicated in

MESENCHYMAL BENIGN TUMORS

as follows:

Lipoma

Disease

benign adipocyte tumor

Prognosis

good

Cytogenetics

various rearrangements involving 12q15 (translocations, inversions, deletions...); reciprocal translocations involve 12q15 with different partners such as chromosomes 1, 2, 3, 7, 10, 11, 13, 15, 17, 21, X; the most frequent anomaly is t(3;12)(q27-28;q15); cryptic rearrangements, such as paracentric inversions not detectable by conventional cytogenetics but detectable by FISH, have been described.

Hybrid/Mutated gene

for t(3;12): HMGIC-LPP (LPP: lipoma preferred partner; 3q27-28); a gene located in 13q, LHFP (lipoma HMGIC fusion partner) was found to be fused with HMGIC in one case of lipoma; one lipoma displayed fusion of HMGA2 exon 4 with a sequence from intron 4, indicating abnormal splicing; HMGA2-CMKOR1 in three cases with aberrations involving 2q35-37 and 12q13-15; HMGA2-NFIB in one lipoma;

Abnormal protein

HMGIC-LPP; the three AT hook domains at the aminoterminal of HMGIC are fused to the LIM domain of LPP; another fusion protein due to the fusion of HMGIC with a putative gene located at 15q24 predicted to encode a protein with a serine/threonine-rich domain has also been described

Oncogenesis

the relevance of the exact role LPP in the HMGA2-LPP fusion is not established yet, but the transactivation functions of the LPP LIM domains is retained in the fusion protein and the fusion protein can function as a transcription factor; the truncation of HMGA2 by itself may have a role in the tumorigenesis

Uterine leiomyoma (uterine fibroids)

Disease

benign mesenchymal tumors

Prognosis

good

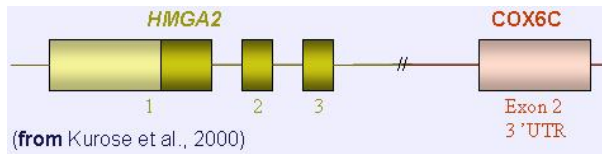
Cytogenetics

approximately 40% of uterine leiomyomas have structural chromosomal rearrangements, about 10% of which involve 12q15 (translocations, inversions, deletions...); the most frequent anomaly is t(12;14)(q15;q23-24)

Hybrid/Mutated gene

in a majority of cases, there is no fusion gene: the breakpoint is located 10 kb up to 100 kb 5' to HMGIC; the recombinational repair gene RAD51B is a candidate to be the partner gene of HMGIC in t(12;14). In two cases (out of 81 primary tumors) exon 7 of RAD51B was fused in frame to either exon 2 or 3 of the HMGA2 gene; in one case with paracentric inversion, HMGIC exon 3 was fused to ALDH2 exon 13 (12q24.1); in one case (no cytogenetic analysis) HMGIC exon 3 was fused to COX6C 3' UTR (8q22-23); in one case, with apparently normal karyotype, exon 3 of HMGIC was fused to retrotransposon-like sequences RTVLH 3' LTRs; three fusion transcripts contained 3' cryptic exonic sequences present in intron 3 of the HMGA2 gene (breakpoints downstream of exons 3 or 4), suggesting that they are due to alternative splicing; one case displayed fusion of the first two exons of

HMGA2 to the 3' portion of the CCNB1IP1/C14orf18/HEI10 gene



Abnormal protein

HMGIC-ALDH2: ALDH2 contribution was only 10 amino acids;

Oncogenesis

HMGIC-ALDH2: it is suggested that the truncation of HMGIC, rather than fusion may be responsible for tumorigenesis; the 3' untranslated region may stabilize the HMGIC messenger RNA

Pleomorphic adenoma of the salivary gland (or mixed salivary gland tumor)

Disease

benign tumors from the major or minor salivary glands

Prognosis

good

Cytogenetics

approximately 12% of pleomorphic adenomas of salivary glands show abnormalities involving HMGIC in 12q15; the most frequent aberration is t(9;12)(p24.1;q15)

Hybrid/Mutated gene

in t(9;12): HMGIC-NFIB fusion; another type of fusion HMGIC-FHIT (3p14.2) has also been described

Pulmonary chondroid hamartoma of the lung

Disease

benign mesenchymal tumors of the lung

Prognosis

good

Cytogenetics

various rearrangements involving 12q15 leading to HMGIC dysregulation; cryptic rearrangements such as paracentric inversions not detectable by

conventional cytogenetics but detectable by FISH have been described.

Hybrid/Mutated gene

in two cases with apparently normal karyotypes, exon 3 of HMGIC was fused to retrotransposon-like sequences RTVLH 3' LTRs; in cases with t(3;12)(q27-28;q14-15) (see lipomas), a fusion of HMGA2-LPP was described; only 1/61 cases with normal karyotype displayed HMGA2-LPP fusion; three cases with rearrangements involving 12q14-15 and 13q12-14 lacked rearrangements of HMGA2-LHFP

Endometrial polyps

Disease

uterine benign tumors

Prognosis

good

Cytogenetics

various rearrangements involving 12q15 leading to HMGIC dysregulation; cryptic rearrangements such as paracentric inversions not detectable by conventional cytogenetics but detectable by FISH have been described; in one case, HMGIC was amplified and overexpressed

Myofibroblastic inflammatory tumor

Disease

benign mesenchymal tumors

Prognosis

good

Cytogenetics

in one case, a complex rearrangement involving chromosomes 12 (in 12q15), 4 and 21 was described

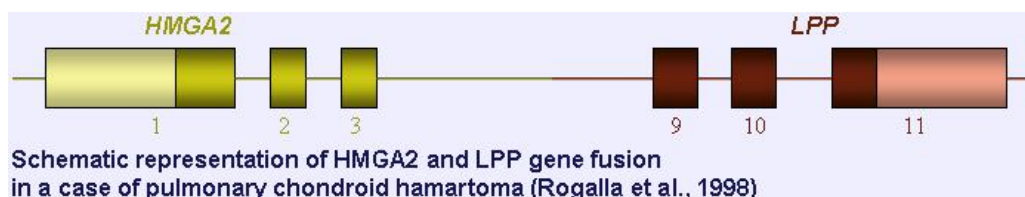
Hybrid/Mutated gene

an aberrant transcript was produced by the fusion of HMGIC exon 3 to an ectopic sequence originating from the third intron of HMGIC

Chondrolipoangioma

Disease

a rare benign type of mesenchymomas composed predominantly of cartilage and adipose tissue with vascular elements and myxoid elements



HMGA2 and MED12 mutations are mutually exclusive and are the two independent factors for tumorigenesis of leiomyoma (Bertsch et al. 2014).

Cytogenetics

One case demonstrated t(12;15)(q13;q26). FISH analysis revealed rearrangement of chromosomes 2, 12 and 15 and HMGA2.

Chondromas

Disease

benign cartilage tumours

Cytogenetics

HMGA2 was expressed in 4/6 soft tissue chondromas (all with 12q-rearrangements cytogenetically), three cases showed truncated (exons 1-3) transcripts, one case displayed a t(3;12)(q27;q15) and RT-PCR demonstrated a HMGA2-LPP fusion transcript composed of HMGA2 exons 1-3 and LPP exons 9-11.

Hyaline vascular Castleman's disease

Cytogenetics

one case with der(6)t(6;12)(q23;q15)del(12)(q15) is described.

Hybrid/Mutated gene

a combined immunologic-cytogenetic approach demonstrated HMGA2 rearrangement in follicular dendritic cells

Prolactinoma

Disease

prolactin-secreting pituitary adenoma, non-metastasizing

Cytogenetics

trisomy 12 nonrandom finding in pituitary adenomas

Hybrid/Mutated gene

HMGA2 locus amplified in 7/8 prolactinomas

Aggressive angiomyxoma of the vulva

Disease

myxoid mesenchymal neoplasm

Prognosis

infiltrative neoplasm, locally destructive recurrences, no metastatic potential

Cytogenetics

one case displayed t(8;12)(p12;q15)

Hybrid/Mutated gene

FISH demonstrated a breakpoint 3' of the gene, the tumour expressed HMGA2

MALIGNANT TUMORS as follows:

Well-differentiated liposarcoma

Disease

malignant adipocyte tumor; peripheral or retroperitoneal location

Prognosis

rather good; borderline malignancy; locally aggressive, rarely metastasizes

Cytogenetics

supernumerary ring or giant marker chromosomes containing 12q14-15 amplification (surrounding MDM2); HMGIC is frequently amplified together with MDM2; rearrangement of HMGA2, in addition to amplification has been described

Hybrid/Mutated gene

ectopic sequences from 12q14-15, 1q24, 11q14, and chromosome 2 was shown to be fused to HMGA2 exon 2 or 3

Uterine leiomyosarcoma

Disease

malignant counterpart of uterine leiomyoma

Prognosis

poor

Cytogenetics

12q13-15 region is recurrently amplified

Hybrid/Mutated gene

HMGA2 amplified within this region

Osteosarcoma

Disease

malignant tumor

Hybrid/Mutated gene

in one osteosarcoma cell line (OsA-CI) the three DNA binding domains of HMGIC fused to the keratan sulfate protein glycan gene LUM (12q22-23); LUM was fused out of frame, and only 3 amino acids were fused to HMGIC; in addition, the rearranged gene was amplified

Myelofibrosis with myeloid metaplasia

Disease

rare chronic myeloproliferative disorder

Prognosis

variable

Cytogenetics

one case with t(4;12)(q32;q15) and one case with t(5;12)(p14;q15)

Hybrid/Mutated gene

FISH analysis suggested breakpoint in HMGA2, RT-PCR revealed that HMGA2 is expressed in blood mononuclear cells from patients with this disease

Acute lymphoblastic leukaemia

Disease

Heterogenous disease that arises in precursor B or T cells

Cytogenetics

One case with a t(9;12)(p22;q14), frequent deletions at 12q14.3

Hybrid/Mutated gene

t(9;12): FISH analysis indicated a breakpoint in the 5' region of the gene, RT-PCR showed overexpression of HMGA2 lacking the carboxyterminal tail; deletions covering the 5' end of HMGA2

High-grade serous carcinoma of the fallopian tubes

Disease

Serous carcinoma arising from fallopian tube secretory epithelia.

Oncogenesis

Overexpression of HMGA2 regulated by several genetic mechanism, including CTNNB1 (β - Catenin), TGF- β , miRNAs. Currently well defined miRNAs including let-7 and MIR-182.

MiR-182 promotes HMGA2 expression through negative regulation of BRCA1 (Moskwa et al. 2011, Liu et al. 2012).

HMGA2 regulates several EMT genes including STC2 and LUM (Wu et al. 2011).

Overexpression of HMGA2 is associated with early tumorigenesis, tumor cell proliferation, invasion and worse outcome through regulation of cell cycle, epithelial to mesenchymal transition (Wu et al. 2011).

Pancreatic carcinoma

Disease

Pancreatic ductal carcinoma.

Oncogenesis

Overexpression of HMGA2 promote EMT by regulation of SNAIL, SLUG, SIP1, TCF3 (E12/E47), and ZEB1 (Watanabe et al. 2009).

HMGA2 nuclear immunoreactivity correlates positively with lymph node metastases and high tumor grade (Hristov et al. 2009).

Breast Cancer

Disease

Serous carcinoma arising from fallopian tube secretory epithelia.

Oncogenesis

HMGA2 gene and protein are highly expressed in metastatic breast cancer cells. HMGA2 as an important regulator of PAR1-mediated invasion.

Inhibition of PAR1 signaling suppresses HMGA2-driven invasion in breast cancer cells (Yang et al. 2015).

Colon Cancer

Disease

Colonic adenocarcinoma.

Oncogenesis

HMGA2 delays the clearance of H2AFX(γ -H2AX) in colon cancer.

Overexpression of HMGA2 is associated with metastasis and unequivocally occurred in parallel with reduced survival rates of patients with colorectal carcinoma (Wang et al. 2011).

Lung Cancer

Disease

Non-small-cell lung cancer (NSCLC)

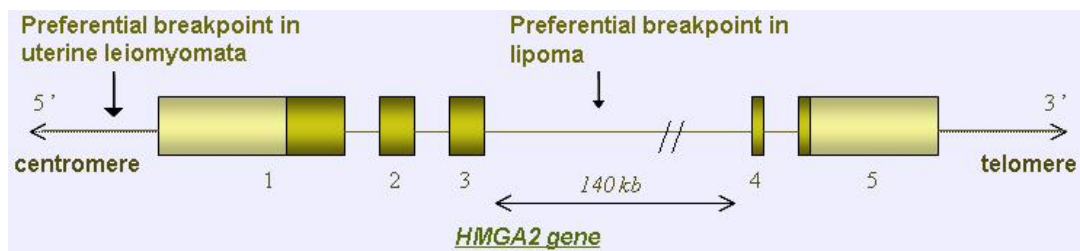
Oncogenesis

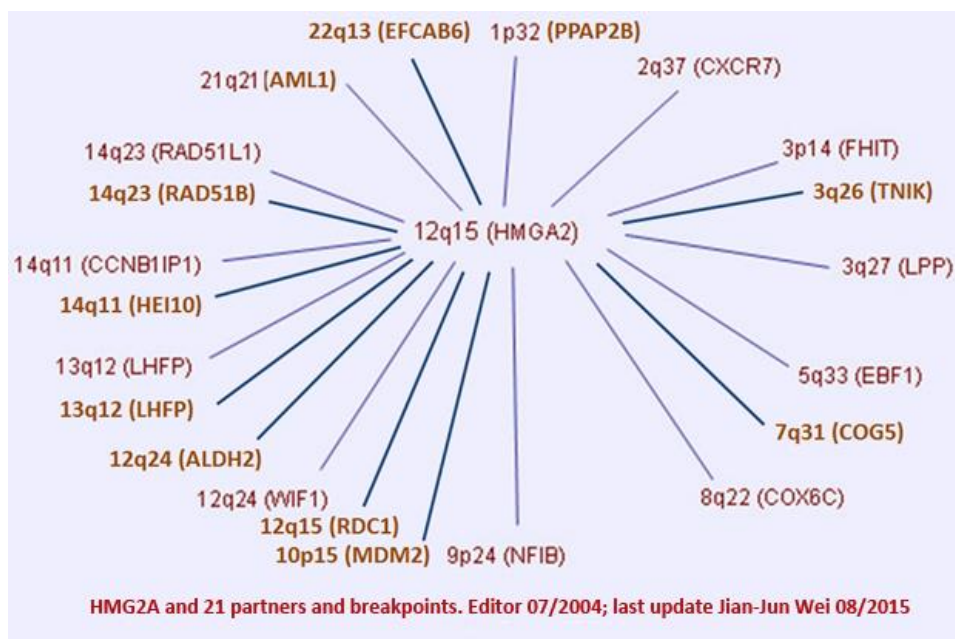
HMGA2 can operate as competing endogenous RNA (ceRNA) for the let-7 microRNA (miRNA) family, suggesting that Hmga2 affects let-7 activity by altering miRNA targeting.

HMGA2 promotes the transformation of lung cancer cells independent of protein-coding function. Tgfbr3 expression is regulated by the Hmga2 ceRNA through differential recruitment to Argonaute 2 (AGO2), and TGF- β signalling driven by Tgfbr3 is important for Hmga2 to promote lung cancer progression (Kumar et al. 2014).

Breakpoints

See below.





Up to 21 partners have a breakpoint with HMGA2 are summarized. The majority of this non-random translocations were found to be in mesenchymal neoplasia (Wu and Wei 2013).

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