Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Mini Review

HMGIC (High mobility group protein isoform I-C)

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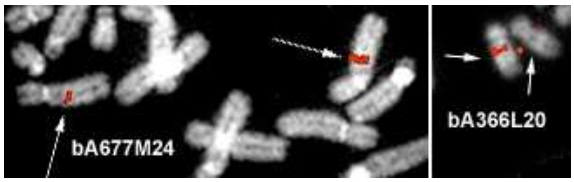
Identity

HGNC (Hugo): HMGIC

Location: 12q15

Local order: Telomeric to CDK4, centromeric to MDM2.



Probe(s) - Courtesy Mariano Rocchi.

DNA/RNA

Description

5 exons, spans approximately 160 kb; the size of intron 3 is 140 kb.

Transcription

RNA: 4.1 kb.

Protein

Description

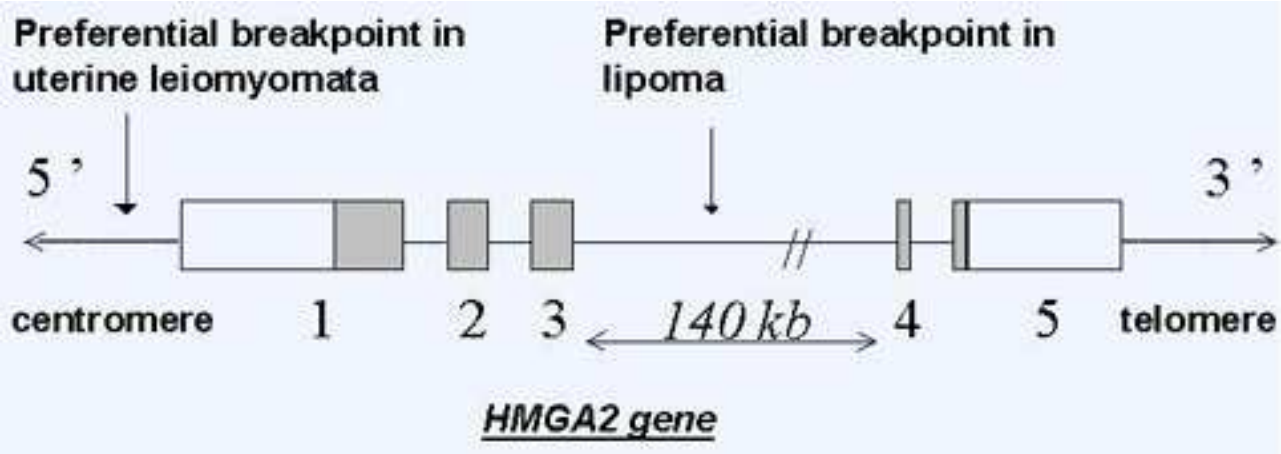
109 amino acids; three DNA binding domains (AT hooks) linked to the carboxy-terminal acidic domain that does not activate transcription.

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.

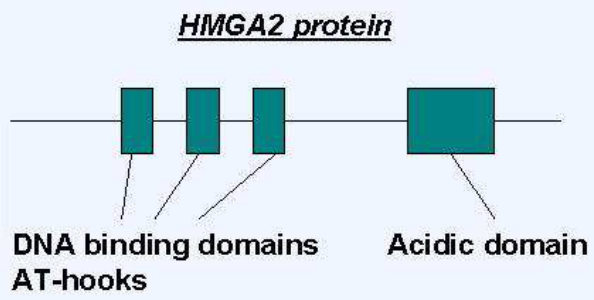
Localisation

Nuclear.



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.

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, 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 prefered 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.

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 HMGIC-LPP fusion is not established yet; the truncation of HMGIC may have a role in the tumorigenesis.

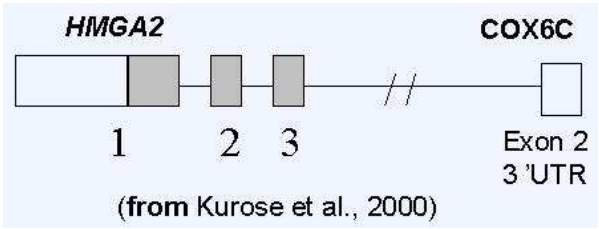
Uterine leiomyoma (uterine fibroids)

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 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.



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.

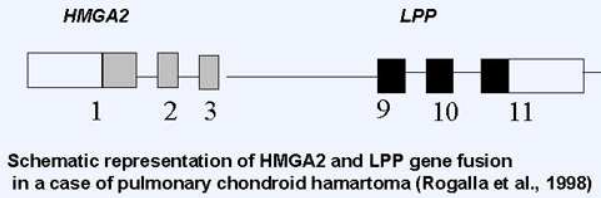
Pulmonary chondroid hamartoma of the lung

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 five cases with t(3;12)(q27;q15) (see lipomas), a fusion HMGIC-LPP was described.



Schematic representation of HMGA2 and LPP gene fusion in a case of pulmonary chondroid hamartoma (Rogalla et al., 1998)

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.

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; in two cases, a rearrangement of HMGIC, in addition to amplification has been described.

Hybrid/Mutated gene
In one case an ectopic sequence from unknown origin was shown to be fused to HMGIC exon 3.

Osteosarcoma

Disease
Malignant tumor.

Hybrid/Mutated gene
In one osteosarcoma cell line (OsA-Cl) 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.

References

Ashar HR, Fejzo MS, Tkachenko A, Zhou X, Fletcher JA, Weremowicz S, Morton CC, Chada K. Disruption of the architectural factor HMGI-C: DNA-binding AT hook motifs fused in lipomas to distinct transcriptional regulatory domains. Cell. 1995 Jul 14;82(1):57-65

Kazmierczak B, Hennig Y, Wanschura S, Rogalla P, Bartnitzke S, Van de Ven W, Bullerdiek J. Description of a novel fusion transcript between HMGI-C, a gene encoding for a member of the high mobility group proteins, and the mitochondrial aldehyde dehydrogenase gene. Cancer Res. 1995 Dec 15;55(24):6038-9

Schoenmakers EF, Wanschura S, Mols R, Bullerdiek J, Van den Berghe H, Van de Ven WJ. Recurrent rearrangements in the high mobility group protein gene, HMGI-C, in benign mesenchymal tumours. Nat Genet. 1995 Aug;10(4):436-44

Zhou X, Benson KF, Ashar HR, Chada K. Mutation responsible for the mouse pygmy phenotype in the developmentally regulated factor HMGI-C. Nature. 1995 Aug 31;376(6543):771-4

Kazmierczak B, Pohnke Y, Bullerdiek J. Fusion transcripts between the HMGIC gene and RTVL-H-related sequences in mesenchymal tumors without cytogenetic aberrations. Genomics. 1996 Dec 1;38(2):223-6

Kools PF, Van de Ven WJ. Amplification of a rearranged form of the high-mobility group protein gene HMGIC in OsA-CI osteosarcoma cells. Cancer Genet Cytogenet. 1996 Oct 1;91(1):1-7

Petit MM, Mols R, Schoenmakers EF, Mandahl N, Van de Ven WJ. LPP, the preferred fusion partner gene of HMGIC in lipomas, is a novel member of the LIM protein gene family. Genomics. 1996 Aug 15;36(1):118-29

Schoenberg Fejzo M, Ashar HR, Krauter KS, Powell WL, Rein MS, Weremowicz S, Yoon SJ, Kucherlapati RS, Chada K, Morton CC. Translocation breakpoints upstream of the HMGIC gene in uterine leiomyomata suggest dysregulation of this gene by a mechanism different from that in lipomas. Genes Chromosomes Cancer. 1996 Sep;17(1):1-6

Wanschura S, Dal Cin P, Kazmierczak B, Bartnitzke S, Van den Berghe H, Bullerdiek J. Hidden paracentric inversions of chromosome arm 12q affecting the HMGIC gene. Genes Chromosomes Cancer. 1997 Apr;18(4):322-3

Hess JL. Chromosomal translocations in benign tumors: the HMGI proteins. Am J Clin Pathol. 1998 Mar;109(3):251-61

Rogalla P, Kazmierczak B, Meyer-Bolte K, Tran KH, Bullerdiek J. The t(3;12)(q27;q14-q15) with underlying HMGIC-LPP fusion is not determining an adipocytic phenotype. Genes Chromosomes Cancer. 1998 Jun;22(2):100-4

Gattas GJ, Quade BJ, Nowak RA, Morton CC. HMGIC expression in human adult and fetal tissues and in uterine leiomyomata. Genes Chromosomes Cancer. 1999 Aug;25(4):316-22

Kazmierczak B, Dal Cin P, Sciot R, Van den Berghe H, Bullerdiek J. Inflammatory myofibroblastic tumor with HMGIC rearrangement. Cancer Genet Cytogenet. 1999 Jul 15;112(2):156-60

Schoenmakers EF, Huysmans C, Van de Ven WJ. Allelic knockout of novel splice variants of human recombination repair gene RAD51B in t(12;14) uterine leiomyomas. Cancer Res. 1999 Jan 1;59(1):19-23

Anand A, Chada K. In vivo modulation of Hmgic reduces obesity. Nat Genet. 2000 Apr;24(4):377-80

Arlotta P, Tai AK, Manfioletti G, Clifford C, Jay G, Ono SJ. Transgenic mice expressing a truncated form of the high mobility group I-C protein develop adiposity and an abnormally high prevalence of lipomas. J Biol Chem. 2000 May 12;275(19):14394-400

Kurose K, Mine N, Doi D, Ota Y, Yoneyama K, Konishi H, Araki T, Emi M. Novel gene fusion of COX6C at 8q22-23 to HMGIC at 12q15 in a uterine leiomyoma. Genes Chromosomes Cancer. 2000 Mar;27(3):303-7

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