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 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.

**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 recombination 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.

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


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