American Journal of Pathology, Vol. 151, No. 1, July 1997

Short Communication

Expression of HMGI-C and HMGI(Y) in Ordinary Lipoma and Atypical Lipomatous Tumors

Immunohistochemical Reactivity Correlates with Karyotypic Alterations

Giovanni Tallini,* Paola Dal Cin,† Kerry J. Rhoden,‡ Gennaro Chiapetta,§ Guidalberto Manfioletti,‖ Vincenzo Giancotti,‖ Alfredo Fusco,¶ Herman Van den Berghe,† and Raf Sciot#

From the Departments of Pathology and Internal Medicine,‡ Yale University School of Medicine and John B. Pierce Laboratory,‡ New Haven, Connecticut; the Center for Human Genetics† and the Department of Pathology,# University of Leuven, Leuven, Belgium; Istituto Nazionale dei Tumori di Napoli, Fondazione Senatore Pascale,§ Napoli, Italy; Dipartimento di Biochimica Biofisica e Chimica delle Macromolecole,‖ Università di Trieste, Trieste, Italy; Dipartimento di Medicina Sperimentale e Clinica,¶ Facoltà di Medicina e Chirurgia di Catanzaro, Università di Reggio Calabria, Italy*

The high mobility group proteins (HMGs) are a class of low molecular weight, nonhistone, nuclear proteins that bind DNA and function as transcription cofactors. This class includes the HMGI family members HMGI-C and HMGI(Y). Both are not significantly expressed in differentiated adult tissues, including fat, but their expression is induced in proliferating and transformed cells. Their involvement in the development of lipomatous tumors has been recently demonstrated for HMGI-C, which is encoded by a gene located at 12q15, the chromosomal segment often rearranged in ordinary lipomas. The same chromosomal segment is consistently amplified in the ring and giant marker chromosomes of atypical lipomatous tumors (ALTs), a term used to designate tumors previously labeled as well differentiated liposarcomas or atypical lipomas. The involvement of HMGI(Y) is strongly suspected as the gene coding for HMGI(Y) is located at 6p21, a chromosomal segment rearranged in a subset of ordinary lipomas. HMGI-C or HMGI(Y) protein expression was analyzed immunohistochemically in a group of 39 well differentiated adipose neoplasms (19 lipomas and 20 ALTs) of known karyotype using polyclonal antibodies raised against a recombinant protein (HMGI-C) and against a synthetic peptide (HMGI(Y)). The results of this study demonstrate that HMGI proteins are commonly expressed in well differentiated adipose neoplasms. Seventeen of twenty ALTS (85.0%), all of which had ring or giant marker chromosomes with amplification of 12q13–15, strongly expressed HMGI-C. HMGI-C expression was detected in 7 of 11 ordinary lipomas (63.6%) with alterations at 12q14–15 and in one case with an abnormal karyotype that included double minute chromosomes. HMGI-C immunoreactivity correlates with 12q13–15 chromosomal alterations (P = 0.001). HMGI(Y) reactivity was demonstrated in only two ordinary lipomas: one with 6p21 rearrangement and one with normal karyotype. No significant HMGI(Y) expression was found in the ALT group. The finding of aberrant expression of HMGI proteins in well differentiated adipose neoplasms in association with 12q13–15 and 6p21 chromosomal changes supports the proposed pathogenetic role of this group

Accepted for publication March 27, 1997.

Address reprint requests to Dr. Giovanni Tallini, Department of Pathology, Yale University School of Medicine, PO Box 208070, New Haven, CT 06520-8070.

of proteins in the development of adipose tissue tumors. (Am J Pathol 1997, 151:37–43)

The high mobility group proteins (HMGs) are a class of nonhistone, relatively small nuclear proteins that bind DNA and function as general transcription regulatory proteins. They lack activation domains and have little specificity in binding but are believed to be involved in the organization of chromatin at the time of DNA transcription providing for the correct steric arrangement of other transcription factors as well as of the basic transcription machinery. They have therefore been referred to as architectural transcription factors.[1] The HMGI family, consisting of HMGI-C and HMGI(Y), represents a distinct subgroup. The genes coding for the HMGI(Y)[2] and HMGI-C[3] proteins have been molecularly cloned and their structure elucidated.[4–7] Both are expressed in the developing embryo but are not detectable at any significant level in adult tissues,[2,3,8–11] including fat.[10] Both are expressed in tumors and transformed cell lines.[12–17] Inactivation of the HMGI-C gene prevents cell transformation in experimental models[18] and induces hypoplasia of mesenchymal tissues (with a specific deficit in the development of adipose tissue).[11]

HMGI(Y) and HMGI-C are localized at 6p21[6] and 12q15,[19] respectively. These chromosomal sites are often rearranged in benign mesenchymal tumors, including uterine leiomyoma, pulmonary chondroid hamartoma, and lipoma.[20] The involvement of HMGI-C in the development of lipomas has been recently proposed, as aberrant fusion transcripts with other genes have been identified in several lipoma cell lines and tissue samples.[4,19,21] However, the overall prevalence of HMGI-C activation in lipomas is unknown. Involvement of HMGI(Y) is strongly suspected as 6p21, the chromosomal region where HMGI(Y) is located, is rearranged in a subset of lipomas.[20,22] In this respect, lipomas are analogous to pulmonary chondroid hamartoma, an uncommon tumor for which the association between cytogenetic changes at 12q15 and 6p21 and alterations of HMGI-C and HMGI(Y), respectively, has also been recently demonstrated.[23,24]

Atypical lipomatous tumor (ALT, a term that encompasses tumors previously labeled as well differentiated liposarcoma and atypical lipoma)[25] are cytogenetically characterized by ring and giant marker chromosomes[22,25] with amplification of the 12q13–15 chromosomal region.[26] Within this chromosomal region, which is amplified in a variety of human sarcomas, discontinuous amplification units have been mapped and include the MDM2 and CDK4 gene loci.[27–30] As HMGI-C is located at 12q13–15, it may also be activated and therefore play a role in the development of ALT in addition to that played in the development of their benign counterpart, ordinary lipoma.

In this context, to further investigate the role of HMGI proteins in the development of adipose tissue tumors, we analyzed HMGI-C and HMGI(Y) protein expression in a series of well differentiated adipose neoplasms. This included a representative set of lipomas of known karyotype and a set of ALTs in which the characteristic 12q13–15 amplification was previously demonstrated.[26] The objectives of the study were to determine whether 1) HMGI proteins are expressed in well differentiated adipose neoplasms, 2) any correlation could be made with the cytogenetic alterations, and 3) the expression pattern in ordinary lipomas differs from that in ALT, their malignant counterpart.

Materials and Methods

Selection of Cases

A total of 39 adipose tissue tumors from 36 patients (3 patients had 2 independent tumors) were selected for this study. All of the tumors were diagnosed and cytogenetically investigated at the University Hospital of the Catholic University of Leuven (Belgium). The original diagnostic slides were reviewed blindly without knowledge of the previous histological diagnosis and karyotype. Nineteen tumors were classified as ordinary lipomas and reflected the principal cytogenetic lipoma subgroups (normal karyotype, 12q15 involvement, 6p21 involvement, and 13q14 involvement).[20,22] The following designations were used to indicate the relevant karyotypic alterations: ring (R), supernumerary ring chromosomes and/or giant marker chromosomes; 12q, aberrations involving the chromosome segment 12q13–15; 6p, aberrations involving the chromosomal site 6p21; 13q, aberrations involving any part of the long arm of chromosome 13; 8q, aberrations involving chromosome segment 8q11–13; other, aberrations not falling into any of the groups listed above; normal (N), normal karyotype (see Tables 1 and 2). Twenty tumors were classified as ALT (traditionally labeled well differentiated liposarcoma or atypical lipoma), and all exhibited a supernumerary ring or giant marker chromosome, which characterizes this specific subtype of adipose tissue tumor.[25] The ALT cases included in this study were previously studied by fluorescent *in situ* hybridization (FISH) using the microclone library ML12q1315 as a molecular probe

for the 12q13–15 chromosomal region.[26] FISH analysis demonstrated amplification of 12q13–15 in all tumor cases.

Immunohistochemistry

Representative formalin-fixed, paraffin-embedded sections were processed for immunohistochemistry according to established techniques in our laboratory.[31] The HMGI-C antibodies were raised in rabbit against the recombinant murine HMGI-C protein.[13] Given the high degree of homology between mouse and human HMGI-C, the antibodies also recognize the human protein.[13] At the dilution used in this study, no significant cross-reactivity was observed with HMGI(Y). The HMGI-C antibodies were used at a 1:400 dilution. Before incubation with the HMGI-C antibodies, histology sections were pretreated with 0.6 mg of Pronase (Sigma Chemical Co., St. Louis, MO) for 5 minutes. The antibodies against HMGI(Y) were developed against a HMGI(Y)-specific synthetic peptide corresponding to the amino-terminal portion of the molecule.[13] They were used at a 1:100 dilution. Negative controls were performed by incubating the histology sections with an unrelated nuclear antibody against human papilloma virus (Dako Corp., Carpinteria, CA) according to the specifications provided by the manufacturer. Immunohistochemistry results were analyzed without knowledge of the cytogenetic data. Nuclear staining for HMGI-C or HMGI(Y) was observed in a variable proportion of the neoplastic adipocytes. The number of positive cells was counted in 20 high-power fields (×40) for each histology section and quantified as a percentage. Positive cases were divided into percentile groups according to the extent of tissue reactivity. Only cases in which there was positive staining in greater than 10% of the neoplastic adipocyte nuclei were scored as positive. The significance of the immunohistochemical data was statistically evaluated. The Fisher's exact test was used to determine the association between HMGI-C reactivity and 12q13–15 aberrations as well as that between HMGI-C and the morphological diagnosis (ALT *versus* ordinary lipoma). Statistical comparison of the degree of positivity between ALT and the lipoma group was carried out by assigning a rank number to the percentile range (0 to 10% = 1, 11 to 20% = 2, and so on) and then performing a Student's *t*-test between the two groups.

Table 1. *HMGI Immunoreactivity and Karyotypic Alterations in Atypical Lipomatous Tumors*

Case	HMGI-C	HMGI(Y)	Cytogenetics
1	61–70	–	R, other
2	31–40	–	R, 8q, other
3	–	–	R
4	51–60	–	R
5	31–40	–	R, other
6	–	–	R
7A	81–90	–	R, other
7B	41–50	–	R, other
8	71–80	–	R
9	31–40	–	R
10A	71–80	–	R
10B	31–40	–	R
11	41–50	–	R
12	81–90	–	R
13	71–80	–	R, other
14	21–30	–	R
15	51–60	–	R
16	–	–	R
17	61–70	–	R, other
18	51–60	–	R

Immunohistochemical reactivity is expressed as the proportion of positive cells estimated in percentile groups. Immunoreactivity is compared with the relevant cytogenetic alterations (see Materials and Methods for abbreviations). In cases 7 and 10, recurrent tumors were excised from the same patient and are referred to as samples A and B. –, negative.

Results

The immunohistochemical results, with the proportion of positive cells expressed in percentile groups for each tumor, and the cytogenetic findings are summarized in Table 1 for the ALTs and Table 2 for

Table 2. *HMGI Immunoreactivity and Karyotypic Alterations in Ordinary Lipomas*

Case	HMGI-C	HMGI(Y)	Cytogenetics
1	–	–	12q, 13q, other
2	21–30	–	12q, 13q
3A	–	–	12q
3B	–	–	6p
4	21–30	–	12q, 6p
5	31–40	–	12q
6	–	–	12q
7	21–30	–	12q
8	–	51–60	6p
9	–	–	12q
10	31–40	–	8q, other
11	41–50	–	12q, 13q
12	21–30	–	12q, 13q
13	–	21–30	N
14	–	–	13q
15	–	–	N
16	–	–	N
17	31–40	–	12q
18	–	–	N

Immunohistochemical reactivity is expressed as the proportion of positive cells estimated in percentile groups. Immunoreactivity is compared with the relevant cytogenetic alterations (see Materials and Methods for abbreviations). In case 3, two separate lipomas were resected from the same patient and are referred to as samples A and B. –, negative.

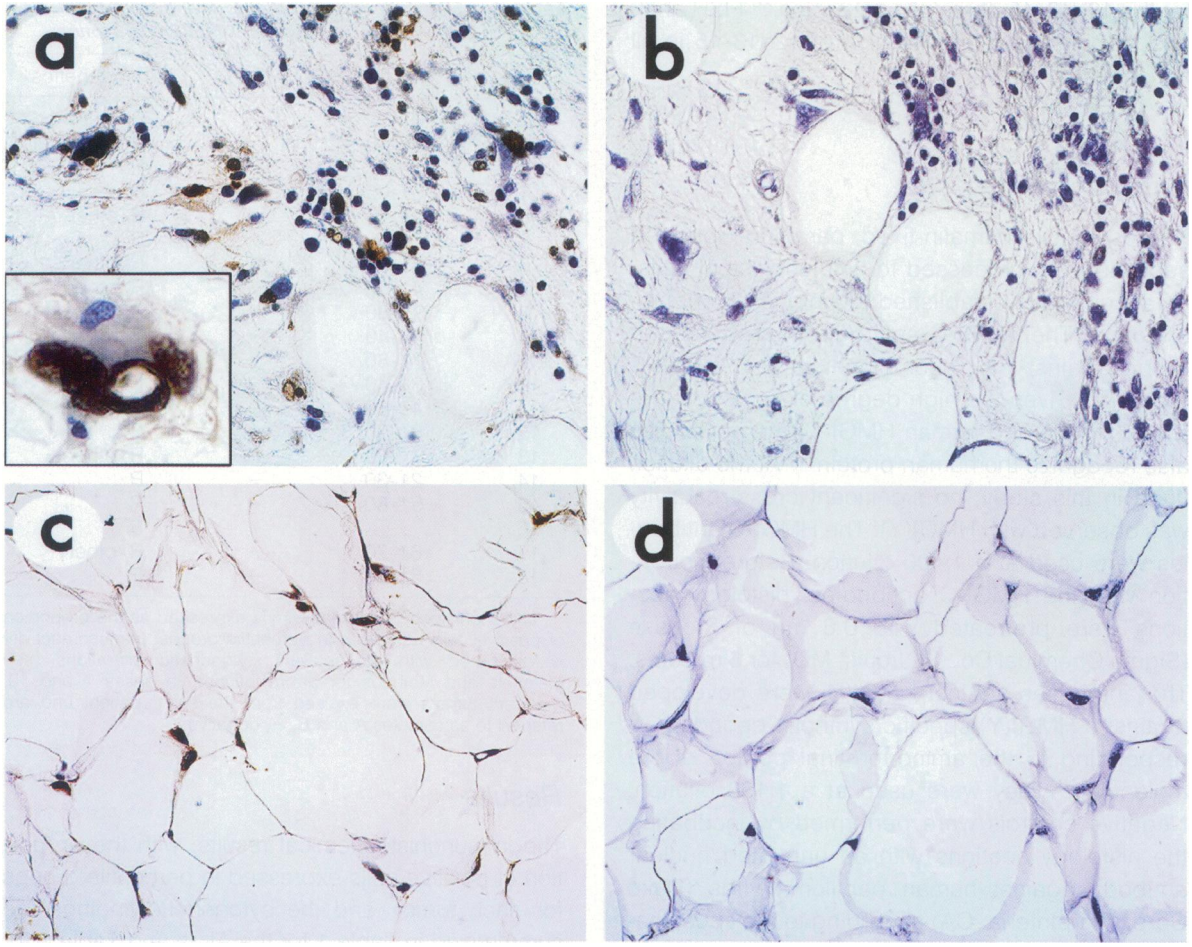

Figure 1. a: *Strong nuclear reactivity for HMGI-C in the neoplastic adipocytes, including multinucleated lipoblasts* (**inset**), *of an atypical lipomatous tumor (case 12); the tumor had 12q13–15 amplification demonstrated by FISH analysis with microclone library ML12q1315 as a molecular probe.* **b:** *Corresponding negative control.* **c:** *Positive nuclear reactivity in the neoplastic adipocytes of an ordinary lipoma (case 8); cytogenetic analysis of the tumor demonstrated t(3;6)(q28;p21).* **d:** *Corresponding negative control. Magnification, ×400.*

the ordinary lipomas. Seventeen of twenty ALTs (85.0%) were positive for HMGI-C, demonstrating a predominantly nuclear pattern of reactivity (Figure 1a). The estimated mean and median values of positivity for the neoplastic adipocytes in the ALTs were both in the 50 to 60th percentile group. No significant HMGI(Y) expression was found in the ALTs. HMGI-C expression was detected in 8 of 19 of ordinary lipomas (42.1%), 7 of which exhibited 12q15–13 rearrangement. The remaining case showed an unusual rearrangement with double minute chromosomes. The estimated mean and median values of positivity for the neoplastic adipocytes in the ordinary lipoma group were both in the 30 to 40th percentile group. HMGI(Y) was positive in 2 of 19 ordinary lipomas (10.5%), one with a normal karyotype and the other with a 6p21 rearrangement (Figure 1c). Unfrequent adipocyte nuclei reacted with HMGI-C or HMGI(Y) antibodies in the remaining nine ordinary lipomas scored as negative. HMGI-C positivity correlated with karyotypic changes, translocation or amplification in the ring chromosomes, involving 12q13–15 (P = 0.001, Fisher's exact test). A significant association was found between HMGI-C positivity and a morphological diagnosis of ALT (P = 0.008, Fisher's exact test). In addition, comparison of the estimated percentages of neoplastic adipocytes immunoreactive for HMGI-C between the positive ALTs and ordinary lipomas demonstrated a greater extent of tissue reactivity in the ALT group (P = 0.002, Student's t-test).

Discussion

This study demonstrates that HMGI proteins are aberrantly expressed in adipose tissue tumors. Although HMGI-C is not normally expressed in mature adipose tissue,[10] fusion mRNA transcripts as a consequence of 12q13–15 rearrangement have been identified in several lipoma cell lines and tissue sam-

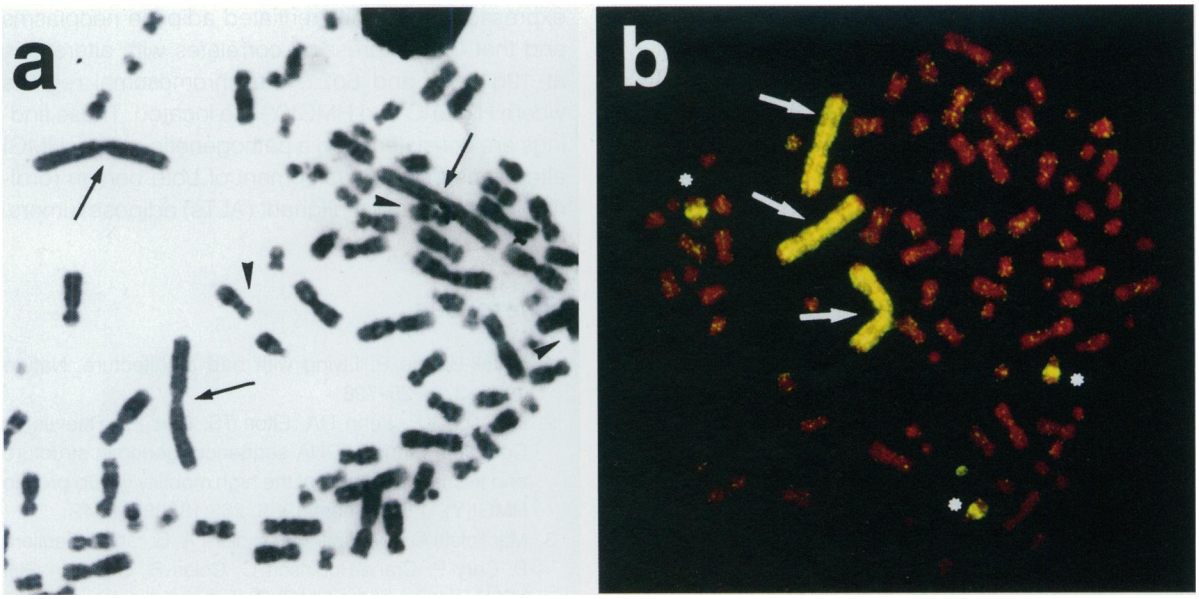

Figure 2. a: *Metaphase spread from an atypical lipomatous tumor (case 7a) exhibiting three long marker chromosomes* (arrows) *and three chromosomes 12* (arrowheads). b: *FISH analysis of a metaphase spread from the same tumor with microclone library ML12q1315 as a molecular probe demonstrating amplification of 12q13–15 in the long marker chromosomes* (arrows) *and painted 12q13–15 regions* (asterisks).

ples.[4,19,21] The translocation partner of HMGI-C on chromosome 3q27–28 has been recently characterized.[21] Such aberrant mRNA would result in chimeric proteins or HMGI-C truncation responsible for tumor development.[4,19,21] In most cases, the breakpoint in the HMGI-C gene occurs in the large (approximately 140 kb)[19,32] third intron of the gene, and the putative chimeric protein includes the three DNA binding domains from exons I to III in the amino-terminal portion of the molecule,[21,32] which are recognized by the antibody used in this study.[13] The aberrant expression of HMGI-C in the majority of the adipose tissue tumors tested in this study is consistent with the proposed role of HMGI-C in the development of ordinary lipomas and demonstrates that HMGI-C activation is a very common occurrence. The expression of HMGI-C, even greater in ALTs compared with ordinary lipomas, indicates that HMGI-C is also activated in this tumor type. All the tumors for which a specific pathogenetic role of HMGI-C has been so far postulated (such as pulmonary chondroid hamartoma, endometrial polyp, and leiomyoma) are benign.[19] This study suggests that activation of HMGI-C may play an important role also in the development of malignant tumors such as ALTs, which can be regarded as the malignant counterpart of ordinary lipoma.

The highly significant ($P = 0.001$) correlation with 12q13–15 chromosomal alterations, both chromosomal translocation in ordinary lipoma and amplification in ALT, is consistent with the view that specific genetic events underlie the increased HMGI-C protein levels observed. In fact, the only tumor to express HMGI-C without cytogenetic alterations at 12q13–15 is an ordinary lipoma with double minute chromosomes, a rare but documented occurrence in benign tumors (P DalCin, S Wanschure, B Kazmierczak, G Tallini, J Bullerdiek, I De Wever, P Moerman, and H Van Den Berghe H, submitted for publication), and it is tempting to speculate that the amplified genetic material in the double minute chromosomes includes the HMGI-C gene. The lack of HMGI-C immunoreactivity in seven tumors (four ordinary lipomas and three ALTs) with 12q13–15 alteration can be explained by an increase in protein expression below the sensitivity threshold of this study, by a fusion protein too abnormal to be recognized by the antibody, by sample bias, or by a combination of the above. An additional explanation is the involvement of other genes located at 12q13–15, a possibility which, in the case of the ALTs, would be supported by the discontinuous amplification of a variety of genomic segments (some including the MDM2 or CDK4 genes) located at 12q13–15.[27–30]

In contrast, HMGI(Y) protein expression is relatively uncommon in adipose tissue tumors, being detectable in only two tumors in this series. The fact that one of them has chromosomal rearrangement of 6p21, where the HMGI(Y) gene is located, indicates that the association between HMGI and cytogenetic changes includes HMGI(Y) as well. A small subset of ordinary lipoma is characterized by 6p21 rearrangements,[20,22] suggesting an analogy with pulmonary

chondroid hamartoma, an uncommon tumor for which the association between cytogenetic changes at 12q15 and 6p21 and alterations of the HMGI-C and HMGI(Y) genes, respectively, has also been recently proposed.[23,24]

The higher prevalence of HMGI-C-positive cases in ALTs ($P = 0.008$) is likely to be related to the greater proportion of ALT cases with 12q13–15 alterations (all of the ALTs had amplified 12q13–15 chromosomal segments) compared with the group of ordinary lipomas that included cases with 13q, 6p, and 8q as well as cases with normal karyotype. It is nevertheless consistent with a correlation between HMGI-C activation, 12q13–15 chromosomal changes, and morphological appearance. Comparison of the proportion of neoplastic adipocytes expressing HMGI-C in the ALTs and ordinary lipomas that scored positive by immunohistochemistry demonstrates an overall greater extent of tissue reactivity in the ALT group ($P = 0.002$). Although the molecular mechanism(s) of HMGI-C activation in ALTs have yet to be elucidated, amplification of 12q13–15, the characteristic cytogenetic feature of ALTs,[22,25,26] suggests that HMGI-C amplification, without ruling out subchromosomal rearrangement of the gene, should be the underlying mechanism. Although the relationship between gene amplification and increased expression of the protein may be complex and is often not completely understood,[33] one may argue that gene amplification may result in high expression levels. In fact, immunohistochemical findings in this study would be compatible with the view that molecular alterations at 12q13–15 with activation of HMGI-C are part of a tumorigenic sequence shared by adipose tissue tumors with (ALT) and without (ordinary lipoma) morphologically identifiable cytological atypia. At one end of the spectrum, the ALT exhibits fully developed morphological and cytogenetic changes (amplification and supernumerary ring chromosomes); at the other end, adipose tissue tumors with very minimal or no (ordinary lipoma) cytological abnormalities share molecular alterations at 12q13–15.[25,34] The correct classification of lipomatous tumors is based on the morphological features, and as such, the diagnosis of ALT, which implies a potentially aggressive clinical behavior, is subject to inter-observer variability and sample bias.[22] The finding of high expression levels of HMGI-C may be a useful adjunct to the morphological observation. Unfortunately, the considerable overlap in HMGI-C expression greatly limits the diagnostic value of such a marker in the discrimination between those tumors that are entirely benign (ordinary lipomas) and those with a potentially aggressive behavior (ALTs).

In summary, this study demonstrates that HMGI proteins, in particular HMGI-C, are often aberrantly expressed in well differentiated adipose neoplasms and that their expression correlates with alterations at 12q13–15 and 6p21, the chromosomal regions where HMGI-C and HMGI(Y) are located. These findings are consistent with a pathogenetic role for HMGI alterations in the development of both benign (ordinary lipomas) and malignant (ALTs) adipose tumors.

References

1. Lovell-Badge R: Living with bad architecture. Nature 1995, 376:725–726
2. Johnson KR, Lehn DA, Elton TS, Barr PJ, Reeves R: Complete murine cDNA sequence, genomic structure and tissue expression of the high mobility group protein HMGI(Y). J Biol Chem 1988, 263:18338–18342
3. Manfioletti G, Giancotti V, Bandiera A, Buratti E, Sautiere P, Cary P, Crane-Robinson C, Coles B, Goodwin GH: cDNA cloning of the HMGI-C phosphoprotein, a nuclear protein associated with neoplastic and undifferentiated phenotypes. Nucleic Acids Res 1991, 19:6793–6797
4. Ashar HR, Schoenberg Fejzo M, 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, 82:57–65
5. Chau KY, Patel UA, Lee KLD, Lam HYP, Crane-Robinson C: The gene for the human architectural transcription factor HMGI-C consists of five exons each coding for a distinct functional element. Nucleic Acids Res 1995, 23:4262–4266
6. Friedman M, Holth LT, Zoghbi HY, Reeves R: Organization, inducible expression and chromosome localization of the human HMG-I(Y) non-histone protein gene. Nucleic Acids Res 1993, 21:4259–4267
7. Manfioletti G, Rustiglio A, Mantovani F, Goodwin GH, Giancotti V: Isolation and characterization of the gene coding for murine high-mobility group protein HMGI-C. Gene 1995, 167:249–253
8. Giancotti V, Bandiera A, Buratti E, Fusco F, Marzari R, Coles B, Goodwin GH: Comparison of multiple forms of the high mobility group I proteins in rodent and human cells, identification of the human high mobility group I-C protein. Eur J Biochem 1991, 198:211–216
9. Giancotti V, Bandiera A, Ciani L, Santoro D, Crane-Robinson C, Goodwin GH, Boiocchi M, Dolcetti R, Casetta B: High-mobility-group (HMG) proteins and histone H1 subtypes expression in normal and tumor tissue of mouse. Eur J Biochem 1993, 211:825–832
10. Rogalla P, Drechsler K, Frey G, Hennig Y, Helmke B, Bonk U, Bullerdiek J: HMGI-C expression patterns in human tissues: implications for the genesis of frequent mesenchymal tumors. Am J Pathol 1996, 149;775–779
11. Zhou S, Benson KF, Ashar HR, Chada K: Mutation responsible for the mouse pygmy phenotype in the developmentally regulated factor HMGI-C. Nature 1995, 376:771–774

12. Bussemakers MJG, Van de Ven WJM, Debruyne FMJ, Schalken J: Identification of high mobility group protein I(Y) as potential progression marker for prostate cancer by differential hybridization analysis. Cancer Res 1991, 51:606–611
13. Chiapetta G, Bandiera A, Berlingieri MT, Visconti R, Manfioletti G, Battista S, Martinez-Tello FJ, Santoro M, Giancotti V, Fusco A: The expression of the high mobility group HMGI(Y) proteins correlates with the malignant phenotype of human thyroid neoplasms. Oncogene 1996, 10:1307–1314
14. Fedele M, Bandiera A, Chiappetta G, Battista S, Viglietto G, Manfioletti G, Casamassimi A, Santoro M, Giancotti V, Fusco A: Human colorectal carcinomas express high levels of high mobility group HMGI(Y) proteins. Cancer Res 1996, 56:1896–1901
15. Giancotti V, Berlingieri MT, Di Fiore PP, Fusco A, Vecchio G, Crane-Robinson C: Changes in nuclear proteins following transformation of rat thyroid epithelial cells by a murine sarcoma retrovirus. Cancer Res 1985, 45:6051–6057
16. Giancotti V, Pani B, D'Andrea P, Berlingieri MT, Di Fiore PP, Fusco A, Vecchio G, Philip R, Crane-Robinson C, Nicolas RH, Wright CA, Goodwin GH: Elevated levels of a specific class of nuclear phosphoroproteins in cells transformed with *ras* and v-*mos* oncogenes and by co-transfection with c-*myc* and polyoma middle T genes. EMBO J 1987, 6:1981–1987
17. Ram TG, Reeves R, Hosick HL: Elevated high mobility group I(Y) gene expression is associated with progressive transformation of mouse mammary epithelial cells. Cancer Res 1993, 53:2655–2660
18. Berlingieri MT, Manfioletti G, Santoro M, Bandiera A, Visconti R, Giancotti V, Fusco A: Inhibition of HMGI-C protein synthesis suppresses retrovirally induced neoplastic transformation of rat thyroid cells. Mol Cell Biol 1995, 15:1545–1553
19. Schoenmakers EFPM, Wanschura S, Mols R, Bullerdiek J, Van den Berghe H, Van de Ven WJM: Recurrent rearrangements in the high mobility group protein gene, HMGI-C, in benign mesenchymal tumors. Nature Genet 1995, 10:436–444
20. Mitelman F: Catalog of Chromosomal Aberration in Cancer, ed 5. New York, Wiley Liss, 1994
21. Petit MMR, Mols R, Schoenmakers EFPM, Mandahl N, Van de Ven WJM: LPP, the preferred fusion partner gene of HMGIC in lipomas, is a novel member of he LIM protein gene family. Genomics 1996, 36:118–129
22. Fletcher CDM, Akerman M, Dal Cin P, DeWever I, Mandahl N, Mertens F, Mitelman F, Rosai J, Rydholm A, Sciot R, Tallini G, Van Den Berghe H, Van De Ven W, Vanni R, Willen H: Correlation between clinicopathologic features and karyotype in lipomatous tumors: a report of 177 cases from the chromosome and morphology (CHAMP) collaborative study group. Am J Pathol 1996, 148:623–630
23. Kazmierczak B, Rosigkeit J, Wanschura S, Meyer-Bolte K, Van de Ven WJM, Kayser K, Krieghoff B, Kastendiek H, Bartnitzke S, Bullerdiek J: HMGI-C rearrangements as the molecular basis for the majority of pulmonary chondroid hamartomas: a survey of 30 tumors. Oncogene 1996, 12:515–521
24. Kazmierczak B, Wanschura S, Rommel B, Bartnitzke S, Bullerdiek J: Ten pulmonary chondroid hamartomas with chromosome 6p21 breakpoints within the HMGI(Y) gene or its immediate surroundings. J Natl Cancer Inst 1996, 88:1234–1236
25. Rosai J, Akerman M, Dal Cin P, DeWever I, Fletcher CDM, Mandahl N, Mertens F, Mitelman F, Rydholm A, Sciot R, Tallini G, Van Den Berghe H, Van De Ven W, Vanni R, Willen H: Combined morphologic and karyotypic study of 59 atypical lipomatous tumors: evaluation of their relationship and differential diagnosis with other adipose tissue tumors (a report of the CHAMP Study Group). Am J Surg Pathol 1996, 20:1182–1189
26. Dal Cin P, Kools P, Sciot R, De Wever I, Van Damme B, Van de Ven W, Van Den Berghe H: Cytogenetic and fluorescence *in situ* hybridization investigation of ring chromosomes characterizing a specific pathologic subgroup of adipose tissue tumors. Cancer Genet Cytogenet 1993, 68:85–90
27. Berner JM, Forus A, Elkahloun A, Meltzer PS, Fodstad O, Myklebost O: Separate amplified regions encompassing CDK4 and MDM2 and human sarcomas. Genes Chromosomes & Cancer 1996, 17:254–259
28. Elkahloun AG, Bittner M, Hoskins K, Gemmill R, Meltzer PS: Molecular cytogenetic characterization and physical mapping of 12q13–15 amplification in human cancers. Genes Chromosomes of Cancer 1996, 17:205–214
29. Nilbert M, Rydholm A, Mitelman F, Meltzer PS, Mandahl N: Characterization of the 12q13–15 amplicon in soft tissue tumors. Cancer Genet Cytogenet 1995, 83:32–36
30. Wolf M, Aaltonen LA, Szymansha J, Tarkkanen M, Elomaa I, Knuutila S: Microsatellite markers as tools for characterization of DNA amplifications evaluated by comparative genomic hybridization. Cancer Genet Cytogenet 1997, 20:1–6
31. Tallini G, Buckley PJ, West AB: Diagnosis of gastrointestinal T-cell lymphomas in routinely processed tissue. J Clin Gastroenterol 1993, 17:57–66
32. Ashar HR, Cerath L, Przybysz KM, Chada K: Genomic characterization of human HMGIC, a member of the accessory transcription factor family found at translocation breakpoints in lipomas. Genomics 1996, 31:207–214
33. Cordon-Cardo C, Latres E, Drobnjak M, Oliva MR, Pollack D, Woodruff JM, Marechal V, Chen J, Brennan MF, Levine AJ: Molecular abnormalities of MDM2 and p53 genes in adult soft tissue sarcomas. Cancer Res 1994, 54:794–799
34. Mandahl N, Akerman M, Aman P, Dal Cin P, De Wever I, Fletcher CDM, Mertens F, Mitelman F, Rosai J, Rydholm A, Sciot R, Tallini G, Van Den Berghe H, Van De Ven W, Vanni R, Willen H: Duplication of chromosome segment 12q15–24 is associated with atypical lipomatous tumors: a report of the CHAMP collaborative study group. Int J Cancer 1996, 67:632–635