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REVIEW ARTICLE

Beyond *MDM2* amplification: chromosomal translocations as diagnostic drivers in adipocytic tumours—a histopathological and molecular reappraisal

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Abstract

Introduction: Cytogenetics analysis of adipocytic tumours revealed varieties of chromosomal translocations beyond MDM2 amplification, so, this report aimed to identify these translocations and recognise the altered genes with their fusion partners. *Materials and Methods:* The materials were collected from different databases including PubMed, and Scopus. *Results:* The collected data revealed that *HMGA2* gene alteration is the initial finding. In addition, *t(9;12)(q33;q14)* is a recurring cytogenetic aberration and engenders an *HMGA2::GSN chimera*. Translocation involving *t(3;12)(q28;q14.3)* is the most common translocation followed by *t(1;12)(p32;q14)* in subset of lipomas. Furthermore, three-way translocation *t(1;4;12)(q21;q27~28;q14~15)* have been reported. In paediatric lipoma, two reports revealed translocations; the first one revealed a translocation involving *t(8;13)(q21;q22)* and *HMGA2::NFIB gene* fusion, and in the second report, the translocation *t(9;12)(p22;q14)* has been identified. Angiolipoma, chondroid lipoma, Myolipoma, hibernoma, spindle cell/pleomorphic lipoma, revealed translocation *t(X;2)(p22;p12),* t(11;16)(q13;p1213), *46,XX,t(9;12)(p22;q14) t(9;11)(q34;q13), t(4;6)(q25;p23)/46,X,tas(Y;21)(p11;p13),* respectively. The presence of *PLAG1* alteration is a fundamental oncogenic event that fused with other partners mainly *COL1A2 gene* and *HAS2,* and rarely with *RAD51L1,* and *COL1A2, RAB2A, COL3A1, PCMTD1, SRSF3, HNRNPC, YWHAZ, CTDSP2, PPP2R2A, BOC, DDX6,, KLF10,* and *KANSL1L, SDCBP, HNRNPA2B1,* other fusions like *EP400::HMGA2* and *FGD6::HMGA2* may be found. Myxoid liposarcoma revealed that the incidence of translocation is *t(12;16)(q13;p11.2) FUS::DDIT3* is quite common, while *t(12;22)(q13;q12) EWSR1::DDIT3* is rare. Recently, *t(12;22)(q13;q12)* has been described. *Conclusion: HMGA2* and *PLAG1* are considered the most important altered genes in most adipocytic tumours subset and lipoblastoma, and identification of their partners is valuable in providing the accurate diagnosis and management especially when the histopathologic diagnosis is unclear.

Keywords: adipocytic tumours, gene, *HMGA2, PLAG1*, partner fusions, lipoblastoma, myxoid liposarcoma

INTRODUCTION

Chromosomal rearrangement (CR) is a disastrous genomic incident that naturally leads to cell death but can frequently play a leading role in cellular alteration leading to carcinogenesis. It is described as a genome deformity in which a chromosome breaks, and either the entire chromosome or a segment of it is missing or is relocated to another chromosome or becomes inverted on the same altered chromosome.[1] The outcome of the break varies according to its location and severity in the setting of dynamically transcribed areas. If the main genes are altered owing to rearrangement, the cell is doomed to die. In other cases, the cell may modify itself to the newly transformed phenotype, leading to modifications in cellular signalling that affect cell cycle and growth,

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leading to the evolution of cancer.[2] CR is a mutation where a chromosome's structure is altered due to loss of a segment (deletion), flipped(inversion), copied (duplication), or moved to another chromosome (chromosomal translocation (CT)). CT is a chromosome abnormality identified by chromosomal rearrangements, which has resulted in the fusion of genes that were initially separated. These "fusion genes" are recognised to be the causes of numerous diseases, including malignant diseases. Two main types of CT are recognised: reciprocal and Robertsonian. The reciprocal translocation refers to two different chromosomes that have exchanged segments with each other. While in a Robertsonian translocation, the whole arm either p or q of different chromosomes links to another at the centromere (the centromere is the pinched area of a chromosome between both arms).[3]

The first fusion gene derived from CT that was dual examined in tumour genesis and as a treatment target is *BCR::ABL*. This fusion gene, from the *t(9;22)(q34;q11),* was observed in chronic myeloid leukaemia (CML) and has been named as "Philadelphia chromosome". The tyrosine kinase inhibitors targeted *BCR::ABL* and produced good responses with clinical benefits against CML. This resulted in the foundation of the molecular-targeting therapy in cancer.[4] Ten years later, a new driver mutation depending on fusion genes derived from CT was recognised in solid tumours such as *EML4::ALK; t(2;5)(p23;q35).*[5] Genetic determination of tumour, whether deletion or CT, is very important as some inhibitor drugs give a good response in translocation and a weak response in mutation, for example, while *ALK*-inhibitors give a good response in *ALK*-related, such as inflammatory myofibroblastic tumours, they give a weak response against mutation in alveolar rhabdomyosarcoma.[6] In addition, one of the mechanisms of molecular therapy is the separation of fused gene chimeras from target promoters, such as the separation of *FUS::CHOP* chimera in cases of ML.[7]

Many CTs have been detected in soft tissue tumours; benign, borderline, and malignant soft tissue tumours.[8] In this report, we aimed to study the histopathological, cytogenetic, and molecular studies of adipocytic tumours with translocation as a series of studies of the entire soft tissue tumours, both histologically and cytogenetically.

In general, most lipoma variants often encompass rearrangements, including conventional lipoma, angiolipoma, chondroid lipoma, myolipoma, spindle cell/pleomorphic lipoma, hibernomas, lipoblastomatosis, lipomatosis of nerve, and myxoid liposarcoma (ML).[9]

Lipoma

A lipoma is a benign adipocytic tumour formed by mature adipocytes. It is the most common mesenchymal tumour in adults, with an equal distribution between male and female incidence; however, it is scarce in children.[10] The most common sites of lipoma are the subcutaneous soft tissue of the upper back, abdominal region, and proximal extremities; however, it may be present in deeply seated soft tissues.[11,12] Histological studies reveal lobules of mature adipocytes separated by pluricellular fibrous septa. Fat necrosis and skeletal muscle fibres may be present. Immunohistochemistry (IHC) and cytogenetic studies reveal that lipoma is positive for *Rb (G3-245)* and *HGMA2,*[12,13] and negative for MDM2, CDK4, and p16.[14]

The differential diagnosis of conventional lipoma includes varieties of lesions such as angiolipoma (AL), spindle cell/pleomorphic lipoma (SC/PL), atypical lipomatous tumour / well-differentiated liposarcoma (ALT/WDLS), and mobile encapsulated adipose tissue (MEAT). AL is composed of mature adipocytes intersected by irregularly branching capillary-sized vessels (containing fibrin thrombi) with different proportions. SC/PL is commonly found in the head, neck, and back, composed of spindles and pleomorphic cells separated by ropy collagen and shows positivity for CD34 and negativity for *Rb. ALT/WDLS* is usually more than 10 cm in size, deep-seated, composed of atypical cells and IHC reveals positivity for MDM2. MEAT is formed by nodules composed of lobules of fat cells surrounded by a dense fibrous capsule with varying degrees of calcification, necrosis, and lipomembranous changes.[15]

Cytogenetics studies reveal structural rearrangement of the *HMGA2* gene or chromosome bands *12q13-q15* and structural rearrangement of the *HMGA1* gene or chromosome band *6p21* with absence of *MDM2,*[16,17] and *CDK4* amplification and loss of giant marker/ring chromosome, and *13p.*[18]

In 2011, Liang *et al.*[18] stated a case of lipoma that revealed a newly balanced translocation linking chromosomes Y and 12. Fluorescence in situ hybridisation (FISH) detected a single signal on normal chromosome 12 but not on the derivative chromosome Y or 12, denoting

a cryptic loss of *12q14.3*, in which *HMGA2* is plotted. IHC revealed negativity for *MDM2* and *CDK4* and overexpression of *HMGA2* in most tumour cells owing to a cryptic chromosomal aberration that affects one of the cytogenetically unchanged *HMGA2* alleles or one of the regulators of *HMGA2* elsewhere.

In 2013, Bianchini *et al*.[19] found that *t(3;12)(q28;q14.3)* is the most common translocation, followed by *t(1;12)(p32;q14)* in a subset of lipomas with detection of overexpression of *HMGA2 mRNA* and protein in all *t(1;12)(p32;q14)* lipomas. In 2016, Agostini *et al*.[20] stated six cases of lipomas, five of which revealed *t*(*4;12)(q27~28;q14~15*) as solitary anomaly, and one lipoma revealed three-way translocation *t*(*1;4;12)(q21;q27~28;q14~15*). Recently, in 2023, Panagopoulos *et al*.[21] stated that in lipoma, *t(9;12)(q33;q14)* is a recurring cytogenetic aberration and engenders an *HMGA2::GSN* chimera. This translocation split the part of *HMGA2* (that encodes *AT-hook* domains) away from the gene's 3'-terminal portion (in which elements that control *HMGA2* expression are represented), as those occur in other *HMGA2* rearrangements of mesenchymal tumours.

Paediatric lipoma

Jin *et al*.[22] reported a case of paediatric lipomas with balanced translocation concerning chromosomes 8 and 13 [*t(8;13)(q21;q22)*] that was spotted by cytogenetic analysis, in addition to small deletions created on *5q21.1* and *8q21.11* which was noticed by array comparative genetic hybridisation but unlike adult lipomas, no rearrangement was noticed on *12q13-q15*. Another case of paediatric lipoma was reported by Lacaria *et al*.[23] who described a 9-year-old male patient with paediatric lipoma and a genetic work-up revealed *HMGA2::NFIB* gene fusion with *t(9;12)(p22;q14)* and provided additional evidence of the association between *NFIB* rearrangement and deep-seated early-onset lipomatous tumours.

Angiolipoma (AL)

AL is a rare benign tumour of soft tissue containing adipocytes and blood vessels. It is usually developed in the second and third decades of life, with male predominance. The usual sites of AL are the trunk and upper extremities and if developed within the central nervous system, it denotes separate lesions encompassing larger vessels.[24] Most cases are sporadic; however, familial predilection is accounted for by 5% with an autosomal dominant mode of inheritance.[25] Histologically, it consists of a lobular pattern formed by mature adipose tissue and branching capillary-sized vessels (more marked at the periphery) interlacing with thin-walled vessels.[26] IHC revealed positive S100, ERG, CD31, CD34, and CD61 and negative for SMA, MART1, CDK4, HHV8, and HMB45.[27]

Cytogenetic studies revealed that most cases have low frequency of *PRKD2* mutations;[28] however, activating *PIK3CA* mutations have been described in sporadic angiolipoma.[29] On the other hand, one tumour has been reported to have *t(X;2)(p22;p12)*.[30] Panagopoulos *et al*.[31] examined 3 cases of angiolipomas cytogenetically and revealed abnormal karyotypes with loss of structural rearrangement of chromosome *13* in all three cases through using G-banding chromosome and FISH analysis using a marketable accessible *RB1* deletion probe. Further analysis of these three cases revealed that the first one has the karyotype *46,XY,-6, del(13)(q14),+mar[cp5]*, the second has *44~45,XY,t(1;10;15)(p21~22;q24;q24),-13[cp5],* and the third karyotype was *43,XX,t(13;22;17)(q12;q13;q22~23)*.[14] Furthermore, FISH analysis revealed deletion of the RB1 probe in the second and third cases, respectively.

Chondroid lipoma (CL)

CL is a rare variant of lipoma with features of immature fat and immature cartilage. It is a painless mass, a slowly growing tumour that occurs in adult women. It is a lobulated, circumscribed, deep-seated tumour, mostly affects the proximal extremities and limb girdles. Histologically, it is usually encapsulated with lobulations, and the lobules are defined by fibrous septa. Each lobule is formed by mature adipocytes, cells demonstrating differentiation towards lipoblasts, admixed with myxohyaline chondroid matrix. These cell components are arranged in nests, cords, and sheets in variable proportions: the cellular patterns are varied in the form of cords, nests, and sheets. Cellular features of adipocytes show vacuolated cytoplasm and peripherally located nuclei giving a signet ring appearance, while those of lipoclastic differentiation may show numerous features such as monotonous undifferentiated cells with minimal cytoplasm or small granular or vacuolated either (uni-or multivacuolated) lipoblasts with scalloping nuclei.[32] Thick-walled vessels are mixed with gaping large thin-walled

vascular spaces.[33] Insignificant nuclear atypia or mitotic activity may be present. Other changes may be present, such as hemosiderin deposition, calcification, fibrosis, and metaplastic bone can be present.[34] Cytogenetic studies of CL revealed three cases with a *t(11;16)(q13;p12– 13),* which fuses the *C11orf95* and *MKL2 genes* [35,36] with one case revealing a ring chromosome in a small piece of metaphases.[37] In addition, Panagopoulos *et al*.[38] studied 12 cases of lipomas including one case of osteochondrolipoma and revealed with a novel *t(12;18)(q14~15;q12~21).*

Myolipoma

Myolipoma is composed of mature adipocytes interlacing with smooth muscle cells. The latter is formed by fascicles of spindle cells with brightly eosinophilic voluminous cytoplasm and blunt-ended nuclei (cigar-shaped nuclei). Very rarely, bizarre multinucleated nuclei, spotted mast cells or lymphocytic cell infiltrates and mitosis may be present.[39] Stroma may be oedematous or hyalinised. Varying small and thick-walled vessels are noted. No definite necrosis has been identified, despite infarction with hyaline change being reported. Overall, the bland cytology is usually seen, but degenerative nuclear atypia may be found. Uncommon features such as round cell morphology, eosinophilic infiltrates, metaplastic bone/cartilage formation, and hemosiderin deposition may be found.[40]

Cytogenetic studies of myolipoma showed a karyotype with a single clonal chromosome abnormality *46,XX,t(9;12)(p22;q14),* which was confirmed by FISH that revealed rearrangement in *HMGA2 (in 12q14)*.[41]

Hibernoma

Histopathological studies of hibernoma revealed an adipocytic tumour with benign features containing uneven proportions of brown fat cells (about 70%) and univacuolated white cells.[42,44] The cells have multivacuolated, eosinophilic granular cytoplasm with a small central nucleus.[44-47] Subtypes of hibernoma were identified, including myxoid, typical, lipoma-like, spindle cell, presence of mast cells, pure brown fat cells as a sole finding, and presence of thick bundles of collagen fibres. Insignificant atypia, mitoses, and necrosis may be present.[48]

Cytogenetics of hibernoma revealed the presence of deletions and translocations affecting *11q13-21*, at *11q13.1*; the site of *MEN1 and AIP gene*.[49] In addition, *UCP1* expression was marked.[50] Two cases were reported with t*(9;11)(q34;q13)*.[42] The first one was identified in 2006 by Turaga *et al*.[51] described a case of a hibernoma with a novel reciprocal translocation between *9q* and *11q* that was valuable in finding the final diagnosis. In 2017, another case was identified to have the same translocation.[40]

Spindle cell / pleomorphic lipoma (SC/PL)

SC/PL is rare benign tumours accounting for 1.5% of all adipocytic tumours. Presently, it is regarded as a structural variant of a solitary neoplasm.[52] It affects the 5th to 8th decades mainly in the subcutaneous tissue of the posterior neck, shoulder, and back.[53-55] Histopathological study reveals that the tumour is formed by mature adipocytes, bland spindle cells (ovoid fusiform nuclei, sometimes with nuclear groove and indefinite bipolar cytoplasmic process), and rope-like hyalinised collagen fibres.[56] In a pleomorphic lipoma, floret cells and multinucleated giant cells are present. The stubby and short spindle cells may show palisading.[57] Commonly, myxoid stroma and interspersed mast cells are seen.[58] Many subtypes have been described: Fat poor and fat free,[59,60] Myxoid,[61] Pseudo angiomatous which reveals nodules of floating tumour on dilated endothelial-lined vascular channels,[62,63] and plexiform.[64] IHC of the tumour shows positivity for CD34, Vimentin, and nuclear loss of *RB1* protein expression.[65,66] In addition, the tumour shows negativity for S100, Keratin, which may show sporadic expression,[67] SOX10, SMA, and Desmin in which sporadic expression may be expressed).[68] ER and STAT6 in 20 - 25%.[69]

The differential diagnosis of SC/PL includes Fibro-lipoma: it is composed of lobules of adipocytes separated by dense fibrous connective tissue, and the consistency of stubby and short cells of spindle cell lipoma is absent. ALT/WDLS: it has a large tumour size, a deeply seated and infiltrative growth pattern. It is formed by atypical stromal cells. IHC and cytogenetic studies reveal positivity towards *MDM2* and *CDK4*, and *MDM2* amplification by FISH. Pleomorphic liposarcoma: it has an infiltrative border and is formed by pleomorphic lipoblasts showing atypical mitoses with an area of necrosis. Cytogenetic studies revealed complex chromosome gains and losses. Myxoid liposarcoma (ML): it usually occurs in younger patients and is formed by small cells with signet ring nuclei and a plexiform capillary network. Cytogenetic study reveals *FUS::DDIT3 gene* rearrangement. Low-grade myxofibrosarcoma:

It is more common in the extremities. It has a different histological grade and varied cellularity. The blood vessels are elongated and curvilinear. Solitary fibrous tumour (especially fat-forming / lipomatous variant): it has marked staghorn and haemangiopericytoma-like vessels. IHC and cytogenetic studies reveal positivity for CD34/STAT6 and *NAB2::STAT6* gene fusion. Mammary type myofibroblastoma: It is formed by short fascicles of monomorphic spindle cells interspersed with thick, coarse collagen bundles. it has a predilection site towards vulvovaginal or inguinoscrotal areas. IHC and cytogenetic studies reveal positivity for Desmin/CD34 and *RB1 (13q14)* deletion/loss of nuclear *RB1* expression. Cellular angiofibroma: it has a predilection site towards the vulvovaginal or inguinoscrotal region. Hyalinised vessels are quite common. IHC and cytogenetic studies reveal positivity for CD34 and *RB1 (13q14)* deletion/loss of nuclear *Rb* expression. Dermatofibrosarcoma protuberans (DFSP): it has a marked storiform growth pattern and infiltrative growth or honeycomb infiltration, with an area of myxoid degeneration may be present. IHC and cytogenetic studies reveal positivity for CD34 and *COL1A1::PDGFB gene* fusion. Schwannoma: it has alternating areas formed by hypercellular areas called Antoni A with marked nuclear palisading and hypocellular myxoid areas called Antoni B. The blood vessels are hyalinised with thickened walls. The tumour is S100 positive. Neurofibroma: it has comma-shaped cells with wavy nuclei, with a variable myxoid to collagenous background. It is CD34-positive fibroblasts and S100-positive Schwann cells.

Molecular /cytogenetics studies of SC/PL reveal monosomy, incomplete chromosomal loss, implying chromosomes *13* and *16*, and an Illustration of the loss of the *RB1* locus.[18,70] In 2001, Domanski *et al*.[71] performed cytogenetic analysis for 7 cases of SC/PL and showed a normal karyotype in two cases, while the remaining five cases revealed clonal chromosomal rearrangements. Those affected cases revealed loss of 13q material, four patients showed loss of the whole chromosome 13, and one case revealed *13q12–13* bands interstitial deletion. In addition, they described a Karyogram plot from subclone of one case as follow: *t(4;6)(q25;p23),46,X,tas(Y;21)(p11;p13), del(13)(q12–13), der(11)t(11;13)(p15;q14).*

Lipoblastomas

Lipoblastoma is a benign myxoid tumour arising in young children that typically proves adipose differentiation. Histopathological studies revealed that the lipoblastomas consist of a lobulated mass formed by sheets of adipocytes containing a network of plexiform vascular pattern in myxoid areas with primitive mesenchymal cells.[72] The central lobular zone is filled by mature adipocytes,[73] while the peripheral zone is filled by immature myxoid cells. In between, fat cells with different stages of maturation are present.[74] Fibro-lipomatous alterations may be seen especially in late resection, with no presence of lipoblasts.[74] Other findings, such as extramedullary haematopoiesis, chondroid metaplasia, floret cells, and chronic inflammation, maybe present.[75]

In 2015, Warren *et al*.[76] studied the difference between lipoblastoma and primitive myxoid mesenchymal tumour of infancy (PMMTI) through studying a rapidly growing neck tumour in a 3-month-old female and found a similarity between lipoblastoma and PMMTI histologically. However, cytogenetic studies established *PLAG1* rearrangement, and the case was diagnosed as lipoblastoma. In addition, they put PMMTI in the differential diagnosis with undifferentiated myxoid lipoblastomas.

Regarding cytogenic studies of lipoblastomas, in 2000, Hibbard *et al*.[77] studied four cases of lipoblastoma and demonstrated that *the COL1A2 gene* and *hyaluronic acid synthase 2* (*HAS2*) promoter regions are fused to the *PLAG1* coding sequence and confirmed that *PLAG1* activation.

In 2001, Gisselsson *et al*.[78] studied 16 cases of lipoblastoma to determine the percentage of *PLAG1* alterations and to evaluate the stages of lipoblastoma differentiation against *PLAG1* genomic alterations and revealed detection of rearrangements of the 8q12 *PLAG1* in 11 cases. Furthermore, they found that *PLAG1* alterations were found in all mesenchymal cells in lipoblastomas, such as mature adipocytes, lipoblasts, fibroblast-like cells, and primitive mesenchymal cells.

In 2013, Deen *et al*.[79] reported lipoblastoma which was initially diagnosed by histopathological study and chromosomal study revealed an unbalanced clonal translocation *t(8;14).* Genomic microarray revealed the breakpoints at 8q12.1 and *14q24.1*, which comprise the *PLAG1* and *RADA51L1* genes. In addition, FISH confirmed *PLAG1::RAD51L1* fusion. These results advocate the role of

RAD51L1 as a substitute partner gene for the *PLAG1* in a lipoblastoma in cases of *8q12* rearrangement.

In 2014, Choi *et al*.[80] study the *8q11-13* region that contains *PLAG1* and explained two different pathways involving *PLAG1*: 1) amplification by multiple copies of a small piece originating from chromosome 8. 2) alteration of the long arm of chromosome 8 resulted in paracentric inversion. Translocations of *8q* as well as splitting of the *PLAG1* probe initiate the process of promoter swapping. Both these anomalies resulted in aberrant *PLAG1* expression. In 2014, Yoshida *et al*.[81] stated that the detection of *PLAG1* gene rearrangement is useful for the diagnosis of lipoblastoma and found three fusion partner genes in relation to *PLAG1* including *HAS2* at *8q24.1, COL1A2* at *7q22*, and *RAD51L1* at *14q24*. In addition, they described two novel fusion genes in lipoblastoma through investigation of six tumours to identify other possible *PLAG1* fusion partners and displayed two novel fusion genes: *RAB2A::PLAG1* in one case and *COL3A1::PLAG1* in three cases. Furthermore, they found the high level of *PLAG1* expression in lipoblastomas 70-150-fold higher than other adipocytic tumours.

In 2018, Abdul-Ghafar *et al*.[82] stated that clonal rearrangements concerning region *8q11 > q13* (*8q12*); the site of *PLAG1* is a characteristic finding of lipoblastomas. In 2019, Zhou *et al*.[83] studied 2 cases of lipoblastomas by FISH analysis, which confirmed the presence of *PLAG1* rearrangement, and the 2 cases were diagnosed as undifferentiated ML. In 2019, Wang *et al*.[84] reported 3 cases of lipoblastomas demonstrating novel genetic aberrations comprising *PLAG1*. The first case revealed a high *PLAG1* amplification to up to 50 copies. The second case showed a partial *PLAG1* deletion with the flanking connection breakpoints, including the *5'HAS2'* and *3'PLAG1*. The third case revealed an insertion of *2q31* into *8q11.2* and *8q* to 2q translocation, and the whole newly translocated form onto 12q, leading to parting of the *PLAG1* FISH probe.

In 2019, Nitta *et al*.[85] described a new *PLAG1* fusion partner gene; *BOC::PLAG1*, which consists of the fusion of the 1st exon of the *BOC gene* to either the 2nd or 3rd exon of the *PLAG1 gene*, and found that *PLAG1* expression was 35.7 ± 2.1 times higher in lipoblastoma than in adipocytes. This translocation leads to an activation of the promoter of *BOC,* leading to *PLAG1* overexpression.

In 2020, Lopez-Nunez *et al*.[86] reported rearrangements in 68% cases of lipoblastomas, 60% of cases had *PLAG1*, and 8% were of *HMGA2*. In addition, five novel fusion partners were identified, such as *DDX6:: PLAG1, KLF10::PLAG1* and *KANSL1L:: PLAG1, EP400::HMGA2*, and *FGD6::HMGA2*. Furthermore, IHC revealed positivity in classic and ML. In 2021, Warren *et al*.[87] studied 24 cases of lipoblastoma and divided them into two groups according to presence or absence of *PLAG1* rearrangement in addition to 10 lipomas as control group with no features of lipoblastoma histology or a *PLAG1* rearrangement. IHC using PLAG1, they found that the sensitivity of *PLAG1* IHC was 94% and assumed that *PLAG1* IHC is an inexpensive marker for detecting and may be used as a potential marker to support the diagnosis of lipoblastoma.

In 2021, Fritchie *et al*.[73] studied 13 cases of lipoblastomas, including five cases of fibroblastic tumours and revealed *PLAG1* rearrangements in 13 tumours. RNA sequencing spotted eight fusion *PLAG1* partners; two of which were already identified, such as *CHCHD7* and *COL3A1*, and six partners were novel (*HNRNPC, SRSF3, YWHAZ, PCMTD1, CTDSP2,* and *PPP2R2A*). In 2023, Panagopoulos *et al*.[88] studied five lipomas, one fibrolipoma, and one SC/PL and found that all 7 tumours had rearrangements of chromosome bands *8q11-13*. FISH analyses revealed *PLAG1* rearrangement. RNA sequencing noticed fusion between *SDCBP* and *PLAG1* in a spindle cell lipoma and fusion between *HNRNPA2B1* and *PLAG1* in a lipoma. They settled that *8q11-13* aberrations/*PLAG1*-rearrangements may obviously be a crucial pathogenetic feature of adipocytic neoplasms of various histological types and not just lipoblastomas and advised proposing "*8q11-13/PLAG1*-rearranged lipomatous tumours" for those tumours that were adopted for this category.

In 2024, Strnadová *et al*.[89] stated a case of an adult patient who presented with a soft tissue tumour that showed a *PLAG1* fusion gene. They spotted a new PLAG1 fusion (*H3-3B::PLAG1*) which initially diagnosed as nodular fasciitis.

Lipoblastoma-like tumour

Lipoblastoma-like tumour is a rare tumour that arises in the vulvar region of young women. It is a benign tumour; however, some reports revealed local recurrences and extremely distant metastases.[90] Histopathological study reveals a well-circumscribed lobulated tumour. Cellular

pattern is composed of a combination of mature adipocytes, lipoblasts and spindle cells settled in abundant myxoid stroma encompassing numerous thin-walled capillaries. The differential diagnoses include ML, cellular angiofibroma, and spindle cell lipoma.[91] Mazzucchelli *et al*.[90] studied a case of lipoblastoma-like tumour in a 28-year-old woman that originated in the inguinal region. Histopathological examination displayed myxoid stroma harboring groups of cells containing mature adipocytes, many univacuolated lipoblasts, and spindle cells with fibrillary cytoplasm and numerous branching thin-walled capillaries. IHC revealed positivity for CD34 and negativity for MDM2 and STAT6. FISH was negative for DDIT3. FISH analysis revealed no loss of *RB1*. Accordingly, the term of lipoblastoma-like tumour" has been established.

Lipomatosis

Lipomatosis is a rare disorder of children that occurs below 2 years or adults. It is associated with steroid therapy, obesity, Cushing's disease, and protease inhibitors for HIV. It has resulted from translocation *concerning high-mobility-group protein isoform I-C gene* set on chromosome *12* and the *lipoma preferred partner gene set on chromosome 3*.[92,93]

Myxoid liposarcoma (ML)

ML is a malignant tumour composed of signet ring lipoblasts, primitive non lipogenic mesenchymal cells, and prominent myxoid stroma with a highly distinctive branching vascular pattern. It accounts for about 5% of adult sarcomas. The peak incidence of ML is in the fourth and fifth decades, with no gender predilection.[94] The most common site for ML is in the proximal thigh and tends to be a multifocal[95] but rarely in hand, and foot.[96] Some ML have a significant round cell component, which gives more chance for metastasis, requiring long-term follow-up.[97] Low-grade tumours are less aggressive but have a tendency for recurrence and can metastasize in about 5 - 10% of cases. The prognosis is poor in presence of *CDKN2A* and *TP53* mutations.[98-105]

Histopathological examination of ML Low grade: it is a paucicellular tumour composed of monomorphic, fusiform, or stellate-shaped cells without atypia. Prominent plexiform delicate thin-walled curving and arborising capillaries (chicken wire fencing). Many signet ring lipoblasts, mostly at the periphery of lobules, are seen, which gives the lipoblastoma-like appearance. Mucoid matrix, or the so-called pulmonary oedema pattern, is present, which is loaded by hyaluronic acid that may enlarge, giving the appearance of mucoid pools, which is detected by alcian blue. Metaplastic bone or cartilage can rarely be seen without progressive molecular change. Insignificant mitotic activity may be present.[106,107] Histological Variants of ML include several 10 variants for ML as follows: traditional myxoid, traditional round cell, pseudo acinar, lipoblast-rich, island, lipomatous, stromal hyalinisation, cord-like, nested, chondroid metaplasia, and hemangiopericytoma (HPC)-like, island and nested patterns.[108] High-grade ML is a hypercellular tumour composed of solid sheets of round cells or primitive morphology. These cells are arranged in a back-to-back pattern. This hypercellular pattern should be more than 5% of the sample examined. Immunohistochemistry of ML revealed positivity for Vimentin, S100,[109] DDIT3,[110] SOX11,[111] and negativity for CD34, MDM2.

The differential diagnosis of ML includes the following: WDLS: it can be myxoid and focally identical to ML. It usually has some degree of stromal atypia, but it lacks the chicken wire plexiform vasculature. Cytogenetically, it has chromosome 12q14amplification involving the MDM2 gene and does not have FUS rearrangement as seen in ML. In addition, ML harbors more signet ring lipoblasts. Extraskeletal myxoidchondrosarcoma (EMC): it is composed of cords of epithelioid malignant cells set in a chondromyxoid matrix. Cytoplasmic vacuoles are not present with less prominent vasculature. Immunohistochemical staining is not valuable because both lesions are positive for S100. Cytogenetics can help detect *t(9;22)(q22;q12)* for EMC in most cases that result in an *EWSR1::NR4A3* fusion. Furthermore, due to the presentation of about 2% of *EWSR1* rearrangements, FISH will give positivity for *EWSR1*, which leads to some conflicts. In this case, PCR can be helpful. If this case arises in the lung, primary pulmonary myxoid sarcoma should be put in the differential diagnosis.[112] Lipoblastoma /lipoblastomatosis: It can show a similar histological description to that of ML, but it usually develops in patients older than 5 years old. Cytogenetic study revealed *PLAG1 gene* rearrangements rather than *EWSR1* or *FUS* rearrangements. Lipoblastoma-like tumour of the vulva: it is a special entity that occurs in the vulva and cuts a significant histological similarity with lipoblastoma and ML. It has Rb loss but does not have *PLAG1* or *FUS* rearrangements.[113,114]

DFSP: it is located mainly superficially. IHC and cytogenetic testing show positivity for CD34, and negativity for S100, in addition to translocations *t(17;22)(q22;q13) COL1A1::PDGFB*. Myxoma: It is paucicellular, neither a prominent vascular part nor lipoblasts are present and may be associated with *GNAS* mutations.[115] Myxofibrosarcoma: It occurs in older adults, mainly superficial, has an infiltrative growth pattern, without true cytoplasmic fat vacuoles, has thicker curvilinear blood vessels, frequent nuclear atypia, and mitosis. Pleomorphic liposarcoma (PLS): It is a separate entity that shares a resemblance in name. It is a high-grade sarcoma with scattered atypical lipoblasts, marked atypia. Characteristically, it has a complex karyotype. Round cell sarcomas (Ewing, and Ewing sarcoma family; BCOR::CCNB3, CIC::DUX4). Various round cell sarcomas that have resemblance to high-grade ML. Low-grade areas and lipoblasts can be specifically helpful. IHC and molecular studies are diagnostic.

Molecular and cytogenetic study of ML revealed that most cases have *t(12;16) (q13;p11.2) FUS::DDIT3* and very rarely *t(12;22)(q13;q12) EWSR1::DDIT3* in about 2-5%. *DDIT3* (CHOP). An earlier study by Mrózek *et al*.[115] who performed a cytogenetic study on ten adipocytic tumours, including one case of myxoid liposarcoma which revealed that *t(12;16)* was the only aberration in myxoid liposarcoma. The latter revealed the breakpoints were localized to bands *12q13.3 and 16p11.2*.

Gibas *et al*.[108] studied 9 cases of ML and found a balanced translocation *t(12;16)(q13;p11)* as the only abnormality in 4 cases. Two cases displayed a connection with other abnormalities. Three tumours proved variants of *t(12;16),* implying other chromosomes. A common factor for all 9 cases studied, the *12q13* breakpoint was implicated in rearrangements.

Repeated these molecular alterations with *FUS::DDIT3, t(12;16)(q13;p11.2)* or rarely *EWSR1::DDIT3, t(12;22)(q13;q12)* rearrangements are reported in a group of diseases comprising high-grade lesions, these high-grade lesions such as round cell liposarcoma tend to present with a first metastasis to another soft tissue or bony site or another soft tissue.[116] Knight *et al*.[117] found that *t(12;16)(q13;p11)* is interpreted as a diagnostic marker for ML. They studied four combined myxoid and round cell, six round cell, and three ML for cytogenic analysis and revealed translocation *t(12;16) (q13;p11)* in three round cell lesions, the *CHOP* (later, *DDIT3*) gene in *12q13* was rearranged and fused to the *TLS gene* in area *16p11* resulting in *TLS::CHOP* RNA transcript that was detected by PCR. In 2022, Tirado *et al*.[118] revealed that the rearrangement of *EWSR1::DDIT3* resulted in the formation of *t(12;22)(q13;q12),* which is a rare cytogenetic pathway of the development of round cell liposarcoma. However, most ML is linked to *t(12;16)(q13;p11),* resulting in *FUS::CHOP* and the resulted oncoprotein interim as aberrant transcription factors. All abbreviations are listed in Table 1, and all fusion partners are summarised in Table 2

Discussion and Conclusion

Cytogenetics of Lipoma revealed that *HMGA2* gene or chromosome bands *12q13-q15*, and overexpression of *HMGA2* in most tumour cells is the initial finding. In addition, *t(9;12) (q33;q14)* is a recurring cytogenetic aberration and engenders an *HMGA2::GSN* chimera. Translocation involving *t(3;12)(q28;q14.3)* is the most common translocation followed by *t(1;12)(p32;q14)* in subset of lipomas with detection of overexpression of *HMGA2 mRNA* and protein in all *t(1;12)(p32;q14)* lipomas. Furthermore, three-way translocation *t(1;4;12)(q21;q27~28;q14~15*) have been reported. In paediatric lipoma, two reports revealed translocations; the first one revealed a translocation involving *t(8;13)(q21;q22)* and *HMGA2::NFIB gene* fusion, and in the second report, the translocation *t(9;12)(p22;q14)* has been identified. Cytogenetics of angiolipoma revealed the presence of one tumour to have *t(X;2)(p22;p12).* Chondroid lipoma revealed translocations involving *t(11;16)(q13;p12– 13).* Myolipoma revealed translocation involving *46,XX,t(9;12)(p22;q14).* Hibernoma displayed deletions and translocations affecting *11q13-21,* at *11q13.1*; the site of *MEN1* and *AIP gene*, as well as *t(9;11)(q34;q13).* Spindle cell/ pleomorphic lipoma showed *t(4;6)(q25;p23)*, *46,X,tas(Y;21)(p11;p13), del(13)(q12–13), der(11)t(11;13)(p15;q14).* Lipoblastomas revealed the importance of *PLAG1, which* is a fundamental oncogenic event in lipoblastoma, and its overexpression is a diagnostic tool marker of lipoblastoma. In addition, other partners may be fused, such as the *collagen 1 alpha 2 (COL1A2) gene and hyaluronic acid synthase 2 (HAS2).* Other rearrangement including clonal *t(8;14), PLAG1::RAD51L1, HAS2::PLAG1 and COL1A2::PLAG1, RAB2A::PLAG1, COL3A1::PLAG1, PCMTD1::PLAG1,*

SRSF3::PLAG1, HNRNPC::PLAG1, YWHAZ::PLAG1, CTDSP2::PLAG1 and PPP2R2A, BOC::PLAG1, DDX6:: PLAG1, KLF10::PLAG1 and *KANSL1L:: PLAG1, EP400::HMGA2* and *FGD6::HMGA2, SDCBP::PLAG1, HNRNPA2B1::PLAG1*. Cytogenetics of ML revealed that the incidence of translocation is *t(12;16)(q13;p11.2) FUS::DDIT3* is very common, while *t(12;22) (q13;q12) EWSR1::DDIT3* (DDIT3 was previously known as *CHOP*) is very rare. Recently, *t(12;22)(q13;q12)* has been described.

Conflict of interest

No conflict of interest to declare

Table 1: List of abbreviations

Abbreviation	*Description*
ABL	*Abelson (Abl) tyrosine kinase gene*
BCR	*break point cluster gene*
EML	*Echinoderm microtubule-associated like 4*
ALK	*Anaplastic lymphoma kinase*
Rb	*retinoblastoma protein*
HMGA2	*High Mobility Group AT-hook 2*
MDM2	*Murine Double Minute 2*
CDK4	*Cyclin-Dependent Kinase 4*
P16	*p16INK4a tumour suppressor protein, or CDKN2A, and multiple tumour suppressor 1 (MTS1)*
CD34	*Cluster of Differentiation 34*
IHC	*Immunohistochemistry*
FISH	*Fluorescence in situ hybridisation*
HMGA2 mRNA	*High Mobility Group AT-Hook 2," and the "mRNA" refers to the messenger RNA transcript for this gene*
HMGA2	*High-mobility Group AT-hook 2 gene*
GSN	*Gelsolin (GSN) gene*
HMGA2	*High Mobility Group AT-hook 2 gene and the*
NFIB	*Nuclear Factor I/B (NFIB) gene*
S100	*100% saturated ammonium sulphate*
ERG	*ETS-related Gene*
CD31	*Cluster of Differentiation 31*
CD61	*Cluster of Differentiation 61*
SMA	*smooth muscle actin*
MART1	*Melanoma-associated antigen recognised by T cells*
HHV8	*Human herpesvirus-8*
PRKD2	*Protein Kinase D2*
PIK3CA	*Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*
C11orf95	*Chromosome 11 open reading frame 95*
MKL2	*Myocardin-like protein 2 or myocardin-related transcription factor B (MRTFB)*
MEN1	*Multiple Endocrine Neoplasia, type 1*
AIP	*Aryl Hydrocarbon Receptor-Interacting Protein*
UCP1	*Uncoupling Protein 1*
SOX10	*SRY (sex determining region Y)-box 10*

Table 1: (continued)

Abbreviation	*Description*
ER	*Oestrogen receptor*
STAT6	*Signal Transducer and Activator of Transcription 6*
FUS	*Fused In Sarcoma*
DDIT3	*DNA damage-inducible transcript 3*
NAB2	*NGFI-A binding protein 2 and*
STAT6	*Signal transducer and activator of transcription 6*
COL1A1-PDGFB	*Collagen type I alpha 1 and platelet-derived growth factor beta*
HAS2	*hyaluronic acid synthase 2*
PLAG1	*Pleomorphic adenoma gene 1*
RADA51L1	*DNA repair protein RAD51 homolog 2*
RAB2A	*Ras-related protein Rab-2A*
RAD51B	*RAD51 paralog B*
BOC	*Brother of CDO, or cell adhesion associated, oncogene regulated*
RAB2A	*Ras-related protein Rab-2A*
PCMTD1	*Protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 1*
SRSF3	*Serine And Arginine-Rich Splicing Factor 3*
HNRNPC	*Heterogeneous nuclear ribonucleoprotein C*
YWHAZ	*tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta*
CTDSP2	*CTD small phosphatase 2*
PPP2R2A	*Protein phosphatase 2, regulatory subunit B, alpha*
DDX6	*DEAD-box helicase 6*
KLF10	*Krüppel-like factor 10*
KANSL1L	*KAT8 Regulatory NSL Complex Subunit 1 Like*
EP400	*E1A Binding Protein P400*
FGD6	*FYVE, RhoGEF and PH domain-containing 6*
SDCBP	*syndecan binding protein*
HNRNPA2B1	*heterogeneous nuclear ribonucleoprotein A2/B1*
H3-3B	*H3 histone family member 3B*
TP53	*Tumour protein p53*
CDKN2A	*Cyclin-Dependent Kinase Inhibitor 2A*
EWSR1	*Ewing sarcoma breakpoint region 1*
PDGFB	*Platelet-derived growth factor beta*
GNAS	*Guanine Nucleotide Binding Protein, Alpha Stimulating.*
BCOR::CCNB3	*BCL6 corepressor and Cyclin B3*
CIC::DUX4	*Capicua and Double homeobox protein 4*
CHOP	*C/EBP Homologous Protein*
TLS	*Tertiary Lymphoid Structures*
LPP	*lipoma preferred partner gene*

Table 2: Table summarises the cytogenetic studies of adipocytic tumours in the current work

Subtypes		*Rearrangement or Translocation*	References
Lipoma	2007	*HMGA2(12q13-q15)*	Sirvent *et al*.[15]
	2019	*t(Y-12)*.	Liang *et al*.[18]
	2013	*t(3;12)(q28;q14.3), t(1;12)(p32;q14)*	Bianchini *et al*.[19]
	2016	*t*(*4;12)(q27~28;q14~15*) *t*(*1;4;12)(q21;q27~28;q14~15*).	Agostini *et al*.[20]
	2021	*t(9;12)(q33;q14)*	Panagopoulos *et al*.[21]
	2022	*HMGA1(6p21)*	Vargas *et al*.[16]
	2023	*HNRNPA2B1* and *PLAG1*	Panagopoulos *et al*.[88]
Paediatric lipoma	2011	*t(8;13)(q21;q22)*	Jin *et al*.[22]
	2017	*t(9;12)(p22;q14) HMGA2::NFIB*	Lacaria *et al*.[23]
Angiolipoma	1994	*t(X;2)(p22;p12)*	Mandahl *et al*.[30]
	2018	*43,XX,t(13;22;17) (q12;q13; q22~23)*	Panagopoulos *et al*.[31]
Chondroid lipoma	2013	*t(11;16)(q13;p12– 13)*	Flucke *et al*.[36]
	2015	*t(12;18)(q14~15;q12~21).*	Panagopoulos *et al*.[38]
Myolipoma	2016	*46,XX,t(9;12)(p22;q14),*	Panagopoulos *et al*.[41]
	2017	*t(9;11)(q34;q13)* [43	Shackelford *et al*.[42]
	2006	reciprocal *t* (*9q -11q)*	Turaga *et al*.[51]
Hibernoma	2010	*11q13-21*, at *11q13.1*	Nord *et al*.[49]
	2017	reciprocal *t* (*9q -11q)*	Fukushima *et al*.[40]
Spindle cell / pleomorphic lipoma	2001	*t(4;6)(q25;p23),46,X,tas(Y;21)(p11;p13)*	Domanski *et al*.[71]
	2023	*SDCBP* and *PLAG1 fusion*	Panagopoulos *et al*.[88]
Lipoblastoma	2000	*COL1A2::PLAG1, HUS2::PLAG1*	Hibbard *et al*.[77]
	2001	Rearrangements of the 8q12 *PLAG1*	Gisselsson *et al*.[78]
	2013	unbalanced clonal *t(8;14). PLAG1::RAD51L1*	Deen *et al*.[79]
	2014	Amplification of PLAG1, alteration of the q8	Choi *et al*.[80]
	2014	*PLAG1* with *HAS2* at *8q24.1, COL1A2* at *7q22*, and *RAD51L1* at *14q24* New fusions: *RAB2A::PLAG1, COL3A1::PLAG1*	Yoshida *et al*.[81]
	2018	*8q11 > q13* (*8q12*) clonal rearrangements	Abdul-Ghafar *et al*.[82]
	2019	Presence of *PLAG1* rearrangement	Zhou *et al*.[83]
	2019	*2q31* into *8q11.2* and *8q* to 2q translocation. Amplification (50 copies), partial *PLAG1* deletion	Wang *et al*.[84]
	2019	*BOC::PLAG1*	Nitta *et al*.[85]
	2020	*DDX6:: PLAG1, KLF10::PLAG1* and *KANSL1L:: PLAG1, EP400::HMGA2*, and *FGD6::HMGA2*.	Lopez-Nunez *et al*.[86]
	2021	*PLAG1* IHC high sensitivity	Warren *et al*.[87]
	2021	*New six PLAG! Partners: HNRNPC, SRSF3, YWHAZ, PCMTD1, CTDSP2,* and *PPP2R2A, and two old partners; CHCHD7* and *COL3A1*	Fritchie *et al*.[73]
	2023	rearrangements of chromosome bands *8q11-13*	Panagopoulos *et al*.[88]
	2024	PLAG1 fusion (*H3-3B::PLAG1*)	Strnadová *et al*.[89]

Table 2: (continued)

Subtypes		*Rearrangement or Translocation*	References
Lipomatosis	2012, 2025	*HMGA2::LPP; t(3;12)(q27;q14-q15)*	Singh C[91] Rosmaninho *et al*.[92]
Myxoid liposarcoma	1993	*t(12;16) breakpoint at* bands *12q13.3 and 16p11.2*	Mrózek *et al*.[115]
	1995	*t(12;16)(q13;p11)*	Gibas *et al*.[108]
	1995	*t(12;16)(q13;p11)*	Knight *et al*.[117]
	2022	*EWSR1::DDIT3 t(12;22)(q13;q12)*	Tirado *et al*.[118]
	2025	*FUS::DDIT3, t(12;16)(q13;p11.2)* or rarely *EWSR1::DDIT3, t(12;22)(q13;q12)*	Potterveld and Clay[116]

REFERENCES

1. Hasty P, Montagna C. Chromosomal Rearrangements in Cancer: Detection and potential causal mechanisms. Mol Cell Oncol. 2014 Jul;1(1):e29904.
2. Le Scouarnec, S, & Gribble SM. Characterising chromosome rearrangements: Recent technical advances in molecular cytogenetics. Heredity, 2011;108(1), 75-85.
3. Rowley JD, Le Beau, MM, Rabbitts TH. Chromosomal Translocations and Genome Rearrangements in Cancer; Springer: Cham, Switzerland, 2015; pp. 3–14. ISBN 978-3-319-19982-5.
4. Schiffer CA. BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia. N. Engl. J. Med. 2007, 357, 258–265.
5. Soda M, Choi YL, Enomoto M, *et al*. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561-566.
6. Shaw AT, Kim TM, Crinò L, *et al*. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(7):874-886.
7. Chen M, Xu ES, Leisenring NH, *et al*. The Fusion Oncogene FUS-CHOP Drives Sarcomagenesis of High-Grade Spindle Cell Sarcomas in Mice. *Sarcoma*. 2019;2019:1340261.
8. Renne SL. Lipoma. PathologyOutlines.com. Accessed October 25, 2025. https://www.pathologyoutlines.com/topic/softtissueadiposelipoma.html
9. Rydholm A, Berg NO. Size, site and clinical incidence of lipoma. Factors in the differential diagnosis of lipoma and sarcoma. *Acta Orthop Scand*. 1983;54(6):929-934.
10. 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;12;275(19):14394-400.
11. Ligon AH, Moore SD, Parisi MA, *et al*. Constitutional rearrangement of the architectural factor HMGA2: a novel human phenotype including overgrowth and lipomas. Am J Hum Genet. 2005;76(2):340-348.
12. Dreux N, Marty M, Chibon F, *et al*. Value and limitation of immunohistochemical expression of HMGA2 in mesenchymal tumours: about a series of 1052 cases. Mod Pathol. 2010;23(12):1657-1666.
13. Thway K, Flora R, Shah C, Olmos D, Fisher C. Diagnostic utility of p16, CDK4, and MDM2 as an immunohistochemical panel in distinguishing well-differentiated and dedifferentiated liposarcomas from other adipocytic tumours. Am J Surg Pathol. 2012;36(3):462-9.
14. Burgdorf WH, Hurt MA. Mobile encapsulated adipose tissue (MEAT) of cows and humans: a distinct nonneoplastic entity. Int J Surg Pathol. 2011;19(5):576-82.
15. Sirvent N, Coindre JM, Maire G, *et al*. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumour samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. Am J Surg Pathol. 2007;31(10):1476-89.
16. Vargas AC, Joy C, Cheah AL, *et al*. Lessons learnt from MDM2 fluorescence in-situ hybridisation analysis of 439 mature lipomatous lesions with an emphasis on atypical lipomatous tumour/well-differentiated liposarcoma lacking cytological atypia. Histopathology. 2022;80(2):369-380.
17. Sandberg AA. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumours: lipoma. Cancer Genet Cytogenet. 2004;15;150(2):93-115.
18. Liang CW, Mariño-Enríquez A, Johannessen C, Hornick JL, Dal Cin P. Translocation (Y;12) in lipoma. Cancer Genet. 2011;204(1):53-6.
19. Bianchini L, Birtwisle L, Saâda E, *et al*. Identification of PPAP2B as a novel recurrent translocation partner gene of HMGA2 in lipomas. Genes Chromosomes Cancer. 2013;52(6):580-90.
20. Agostini A, Gorunova L, Bjerkehagen B, Lobmaier I, Heim S, Panagopoulos I. Molecular characterization of the t(4;12)(q27~28;q14~15) chromosomal rearrangement in lipoma. Oncol Lett. 2016;12(3):1701-1704.
21. Panagopoulos I, Andersen K, Brunetti M, *et al*.

Fusion of the High-mobility Group AT-Hook 2 (HMGA2) and the Gelsolin (GSN) Genes in Lipomas With t(9;12)(q33;q14) Chromosomal Translocation. In Vivo. 2023;37(2):524-530.
22. Jin J, Niu J, Kim YM, *et al*. A novel t(8;13)(q21;q22) translocation in a paediatric lipoma. Cancer Genet. 2011;204(11):629-33.
23. Lacaria M, El Demellawy D, McGowan-Jordan J. A rare case of paediatric lipoma with t(9;12)(p22;q14) and evidence of HMGA2-NFIB gene fusion. Cancer Genet. 2017;216-217:100-104.
24. Shekhtman O, Gorozhanin V, Shishkina L. A Rare Case of Brain Angiolipoma Imitating Arteriovenous Malformation: Differential Diagnosis, Surgical Treatment, and Literature Review. World Neurosurg. 2018;114:264-268.
25. Abbasi NR, Brownell I, Fangman W. Familial multiple angiolipomatosis. Dermatol Online J. 2007;27;13(1):3. PMID: 17511936.
26. Dixon AY, McGregor DH, Lee SH. Angiolipomas: an ultrastructural and clinicopathological study. Hum Pathol. 1981;12(8):739-47.
27. Liu YJ, Karamchandani DM. Gastric Angiolipoma: A Rare Entity. Arch Pathol Lab Med. 2017;141(6):862-866.
28. Hofvander J, Arbajian E, Stenkula KG, *et al*. Frequent low-level mutations of protein kinase D2 in angiolipoma. J Pathol. 2017;241(5):578-582.
29. Saggini A, Santonja C, Nájera L, Palmedo G, Kutzner H. Frequent activating PIK3CA mutations in sporadic angiolipoma. J Cutan Pathol. 2021;48(2):211-216.
30. Mandahl N, Höglund M, Mertens F, *et al*. Cytogenetic aberrations in 188 benign and borderline adipose tissue tumours. Genes Chromosomes Cancer. 1994;9(3):207-15.
31. Panagopoulos I, Gorunova L, Andersen K, Lobmaier I, Bjerkehagen B, Heim S. Consistent Involvement of Chromosome 13 in Angiolipoma. Cancer Genomics Proteomics. 2018;15(1):61-65.
32. Kindblom LG, Meis-Kindblom JM. Chondroid lipoma: an ultrastructural and immunohistochemical analysis with further observations regarding its differentiation. Hum Pathol. 1995;26(7):706-15
33. Thomson TA, Horsman D, Bainbridge TC. Cytogenetic and cytologic features of chondroid lipoma of soft tissue. Mod Pathol 1999;12:88–91
34. Hoch B, Hermann G, Klein MJ, Abdelwahab IF. Ossifying chondroid lipoma. Skeletal Radiol. 2008;37(5):475-80.
35. Gisselsson D, Domanski HA, Hoglund M. Unique cytological features and chromosome aberrations in chondroid lipoma. Am J Surg Pathol 1999;23:1300–1304.
36. Flucke U, Tops BB, de Saint Aubain Somerhausen N, *et al*. Presence of C11orf95-MKL2 fusion is a consistent finding in chondroid lipomas: a study of eight cases. Histopathology. 2013;62(6):925-30.
37. Ballaux F, Debiec-Rychter M, De Wever I, Sciot R. Chondroid lipoma is characterized by t(11;16)(q13;p12-13). Virchows Arch. 2004;444(2):208-10.
38. Panagopoulos I, Gorunova L, Bjerkehagen B, Lobmaier I, Heim S. The recurrent chromosomal translocation t(12;18)(q14~15;q12~21) causes the fusion gene HMGA2-SETBP1 and HMGA2 expression in lipoma and osteochondrolipoma. Int J Oncol. 2015;47(3):884-90.
39. Scarpellini F, Pasquinelli G, Damiani S. Miolipoma sottocutaneo con cellule bizzarre: studio morfologico, immunoistochimico e ultrastrutturale di un caso e revisione della letteratura [Subcutaneous myolipoma with bizarre cells: morphological, immunohistochemical and ultrastructural study of a case and review of the literature]. Pathologica. 1997;89(2):163-7.
40. Fukushima M, Schaefer IM, Fletcher CD. Myolipoma of Soft Tissue: Clinicopathologic Analysis of 34 Cases. Am J Surg Pathol. 2017;41(2):153-160.
41. Panagopoulos I, Gorunova L, Agostini A, Lobmaier I, Bjerkehagen B, Heim S. Fusion of the HMGA2 and C9orf92 genes in myolipoma with t(9;12)(p22;q14). Diagn Pathol. 2016;9;11-22.
42. Shackelford RE, Al Shaarani M, Ansari J, Wei E, Cotelingam J. A Twenty-Four-Year-Old Woman with Left Flank Lipoma-Like Hibernoma. Case Rep Oncol. 2017;9;10(2):438-441.
43. AlQattan AS, Al Abdrabalnabi AA, Al Duhileb MA, Ewies T, Mashhour M, Abbas A. A Diagnostic Dilemma of a Subcutaneous Hibernoma: Case Report. Am J Case Rep. 2020;25;21:e921447.
44. Myslicki FA, Rosenberg AE, Chaitowitz I, Subhawong TK. Intraosseous Hibernoma: Five Cases and a Review of the Literature. J Comput Assist Tomogr. 2019;43(5):793-798.
45. Song B, Ryu HJ, Lee C, Moon KC. Intraosseous Hibernoma: A Rare and Unique Intraosseous Lesion. J Pathol Transl Med. 2017;51(5):499-504.
46. AlHmada Y, Schaefer IM, Fletcher CDM. Hibernoma Mimicking Atypical Lipomatous Tumour: 64 Cases of a Morphologically Distinct Subset. Am J Surg Pathol. 2018;42(7):951-957.
47. Tsuda Y, Matsuyama A, Makihara K, *et al*. Nuclear expression of MDM2 in hibernoma: a potential diagnostic pitfall. Virchows Arch. 2021;478(3):527-534.
48. Huang C, Zhang L, Hu X, Liu Q, Qu W, Li R. Femoral nerve compression caused by a hibernoma in the right thigh: a case report and literature review. BMC Surg. 2021;7;21(1):30.
49. Nord KH, Magnusson L, Isaksson M, *et al*. Concomitant deletions of tumour suppressor genes MEN1 and AIP are essential for the pathogenesis of the brown fat tumour hibernoma. Proc Natl Acad Sci U S A. 2010;7;107(49):21122-7.
50. Malzahn J, Kastrenopoulou A, Papadimitriou-Olivgeri I, *et al*. Immunophenotypic expression of UCP1 in hibernoma and other adipose/non adipose soft tissue tumours. Clin Sarcoma Res. 2019;13;9:8.
51. Turaga KK, Silva-Lopez E, Sanger WG, *et al*. A (9;11)(q34;q13) translocation in a hibernoma. Cancer Genet Cytogenet. 2006;15;170(2):163-6.
52. Fletcher CD, Martin-Bates E. Spindle cell lipoma: a clinicopathological study with some original observations. Histopathology. 1987;11(8):803-17.
53. Enzinger FM, Harvey DA. Spindle cell lipoma. Cancer. 1975;36(5):1852-1859.

54. Shmookler BM, Enzinger FM. Pleomorphic lipoma: a benign tumour simulating liposarcoma. A clinicopathologic analysis of 48 cases. Cancer. 1981;1;47(1):126-33.
55. Ko JS, Daniels B, Emanuel PO, *et al*. Spindle Cell Lipomas in Women: A Report of 53 Cases. Am J Surg Pathol. 2017;41(9):1267-1274.
56. French CA, Mentzel T, Kutzner H, Fletcher CD. Intradermal spindle cell/pleomorphic lipoma: a distinct subset. Am J Dermatopathol. 2000;22(6):496-502.
57. Gupta S, Gupta R, Sodhani P. Spindle cell lipoma with predominant nerve sheath tumor-like areas: A potential diagnostic pitfall on aspiration cytology. Diagn Cytopathol. 2015;43(12):1017-9.
58. Michal M, Kazakov DV, Hadravsky L, *et al*. Lipoblasts in spindle cell and pleomorphic lipomas: a close scrutiny. Hum Pathol. 2017;65:140-146.
59. Billings SD, Folpe AL. Diagnostically challenging spindle cell lipomas: a report of 34 "low-fat" and "fat-free" variants. Am J Dermatopathol. 2007;29(5):437-42.
60. Sachdeva MP, Goldblum JR, Rubin BP, Billings SD. Low-fat and fat-free pleomorphic lipomas: a diagnostic challenge. Am J Dermatopathol. 2009;31(5):423-6.
61. Wong YP, Chia WK, Low SF, Mohamed-Haflah NH, Sharifah NA. Dendritic fibromyxolipoma: a variant of spindle cell lipoma with extensive myxoid change, with cytogenetic evidence. Pathol Int. 2014;64(7):346-51.
62. Hawley IC, Krausz T, Evans DJ, Fletcher CD. Spindle cell lipoma--a pseudoangiomatous variant. Histopathology. 1994;24(6):565-9.
63. Zamecnik M, Michal M. Angiomatous spindle cell lipoma: Report of three cases with immunohistochemical and ultrastructural study and reappraisal of former 'pseudoangiomatous' variant. Pathol Int. 2007;57(1):26-31.
64. Zelger BW, Zelger BG, Plörer A, Steiner H, Fritsch PO. Dermal spindle cell lipoma: plexiform and nodular variants. Histopathology. 1995;27(6):533-40.
65. Templeton SF, Solomon AR Jr. Spindle cell lipoma is strongly CD34 positive. An immunohistochemical study. J Cutan Pathol. 1996;23(6):546-50.
66. Chen BJ, Mariño-Enríquez A, Fletcher CD, Hornick JL. Loss of retinoblastoma protein expression in spindle cell/pleomorphic lipomas and cytogenetically related tumours: an immunohistochemical study with diagnostic implications. Am J Surg Pathol. 2012;36(8):1119-28.
67. Mentzel T, Rütten A, Hantschke M, Hornick JL, Brenn T. S-100 protein expressing spindle cells in spindle cell lipoma: a diagnostic pitfall. Virchows Arch. 2016;469(4):435-8.
68. Tardío JC, Aramburu JA, Santonja C. Desmin expression in spindle cell lipomas: a potential diagnostic pitfall. Virchows Arch. 2004;445(4):354-8.
69. Ko JS, Daniels B, Emanuel PO, *et al*. Spindle Cell Lipomas in Women: A Report of 53 Cases. Am J Surg Pathol. 2017;41(9):1267-1274.
70. Bartuma H, Nord KH, Macchia G, *et al*. Gene expression and single nucleotide polymorphism array analyses of spindle cell lipomas and conventional lipomas with 13q14 deletion. Genes Chromosomes Cancer. 2011;50(8):619-32.
71. Domanski HA, Carlén B, Jonsson K, Mertens F, Åkerman M. Distinct cytologic features of spindle cell lipoma. Cancer Cytopathology, 2001;93(6),381-389.
72. Collins MH, Chatten J. Lipoblastoma/ lipoblastomatosis: a clinicopathologic study of 25 tumours. Am J Surg Pathol. 1997;21(10):1131-7.
73. Fritchie K, Wang L, Yin Z, *et al*. Lipoblastomas presenting in older children and adults: analysis of 22 cases with identification of novel PLAG1 fusion partners. Mod Pathol. 2021;34(3):584-591.
74. Morerio C, Nozza P, Tassano E, *et al*. Differential diagnosis of lipoma-like lipoblastoma. Pediatr Blood Cancer. 2009 ;52(1):132-4.
75. Ameloot E, Cordier F, Van Dorpe J, Creytens D. Update of Paediatric Lipomatous Lesions: A Clinicopathological, Immunohistochemical and Molecular Overview. J Clin Med. 2022;31;11(7):1938.
76. Warren M, Turpin BK, Mark M, Smolarek TA, Li X. Undifferentiated myxoid lipoblastoma with PLAG1-HAS2 fusion in an infant; morphologically mimicking primitive myxoid mesenchymal tumour of infancy (PMMTI)--diagnostic importance of cytogenetic and molecular testing and literature review. Cancer Genet. 2016;209(1-2):21-9.
77. Hibbard MK, Kozakewich HP, Dal Cin P, *et al*. PLAG1 fusion oncogenes in lipoblastoma. Cancer Res. 2000;1;60(17):4869-72.
78. Gisselsson D, Hibbard MK, Dal Cin P, *et al*. PLAG1 alterations in lipoblastoma: involvement in varied mesenchymal cell types and evidence for alternative oncogenic mechanisms. Am J Pathol. 2001;159(3):955-62.
79. Deen M, Ebrahim S, Schloff D, Mohamed AN. A novel PLAG1-RAD51L1 gene fusion resulting from a t(8;14)(q12;q24) in a case of lipoblastoma. Cancer Genet. 2013;206(6):233-7.
80. Choi J, Bouron Dal Soglio D, Fortier A, *et al*. Diagnostic utility of molecular and cytogenetic analysis in lipoblastoma: a study of two cases and review of the literature. Histopathology. 2014;64(5):731-40.
81. Yoshida H, Miyachi M, Ouchi K, *et al*. Identification of COL3A1 and RAB2A as novel translocation partner genes of PLAG1 in lipoblastoma. Genes Chromosomes Cancer. 2014;53(7):606-11.
82. Abdul-Ghafar J, Ahmad Z, Tariq MU, Kayani N, Uddin N. Lipoblastoma: a clinicopathologic review of 23 cases from a major tertiary care center plus detailed review of literature. BMC Res Notes. 2018;17;11(1):42.
83. Zhou J, Li X, Cai Y, Wang L, Yang SD. Undifferentiated myxoid lipoblastoma with PLAG1 gene rearrangement in infant. Pathol Res Pract. 2020;216(1):152765.
84. Wang G, Guzman MA, Batanian JR. Three Novel Aberrations Involving PLAG1 Leading to

Lipoblastoma in Three Different Patients: High Amplification, Partial Deletion, and a Unique Complex Rearrangement. Cytogenet Genome Res. 2019;159(2):81-87.
85. Nitta Y, Miyachi M, Tomida A, *et al*. Identification of a novel BOC-PLAG1 fusion gene in a case of lipoblastoma. Biochem Biophys Res Commun. 2019;23;512(1):49-52.
86. Lopez-Nunez O, Alaggio R, Ranganathan S, *et al*. New molecular insights into the pathogenesis of lipoblastomas: clinicopathologic, immunohistochemical, and molecular analysis in paediatric cases. Hum Pathol. 2020;104:30-41.
87. Warren M, Tiwari N, Sy S, Raca G, Schmidt RJ, Pawel B. PLAG1 Immunohistochemical Staining Is a Surrogate Marker for PLAG1 Fusions in Lipoblastomas. Pediatr Dev Pathol. 2022;25(2):134-140.
88. Panagopoulos I, Andersen K, Gorunova L, *et al*. Recurrent 8q11-13 Aberrations Leading to PLAG1 Rearrangements, Including Novel Chimeras HNRNPA2B1::PLAG1 and SDCBP::PLAG1, in Lipomatous Tumours. Cancer Genomics Proteomics. 2023;20(2):171-181.
89. Strnadová M, Balko J, Brož P, Wagenknecht L, Krsková L. Fibromyxoid a Soft Tissue Tumour With PLAG1 Fusion-The First Case in an Adult Patient. Genes Chromosomes Cancer. 2024;63(11):e70011.
90. Mazzucchelli M, Angelico G, Salvatorelli L, *et al*. Lipoblastoma-like tumour of the inguinal region: a close mimicker of myxoid liposarcoma. Pathologica. 2025;117(1):39-44.
91. Singh C. Lipomatosis. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/softtissueadiposelipomatosis.html. Accessed October 14th, 2025.
92. Rosmaninho A, Pinto-Almeida T, Fernandes IC, Machado S, Selores M. Do you know this syndrome? An Bras Dermatol. 2012;87(2):324-5.
93. Muratori F, Bettini L, Frenos F, *et al*. Myxoid Liposarcoma: Prognostic Factors and Metastatic Pattern in a Series of 148 Patients Treated at a Single Institution. Int J Surg Oncol. 2018;16;2018:8928706.
94. Estourgie SH, Nielsen GP, Ott MJ. Metastatic patterns of extremity myxoid liposarcoma and their outcome. J Surg Oncol. 2002;80(2):89-93.
95. Buehler D, Marburger TB, Billings SD. Primary subcutaneous myxoid liposarcoma: a clinicopathologic review of three cases with molecular confirmation and discussion of the differential diagnosis. J Cutan Pathol. 2014;41(12):907-15.
96. Hanna SA, Qureshi YA, Bayliss L, *et al*. Late widespread skeletal metastases from myxoid liposarcoma detected by MRI only. World J Surg Oncol. 2008;18;6:62.
97. Pilotti S, Lavarino C, Mezzelani A, *et al*. Limited role of TP53 and TP53-related genes in myxoid liposarcoma. Tumouri. 1998;84(5):571-7.
98. Löwenthal D, Zeile M, Niederhagen M, *et al*. Differentiation of myxoid liposarcoma by magnetic resonance imaging: a histopathologic correlation. Acta Radiol. 2014;55(8):952-60.
99. Gorelik N, Reddy SMV, Turcotte RE, *et al*. Early detection of metastases using whole-body MRI for initial staging and routine follow-up of myxoid liposarcoma. Skeletal Radiol. 2018;47(3):369-379.
100. Tysome JR, Sandison A, Clarke PM. Myxoid liposarcoma metastatic to the thyroid gland: a case report and literature review. J Laryngol Otol. 2006;120(6):511-3.
101. Fernández-Aceñero MJ, López-Criado P, López-Franco M, Meizoso T, Calvo C. Multicentric myxoid liposarcoma: report of two cases. World J Surg Oncol. 2007;10;5:139.
102. Yokouchi M, Nagano S, Kijima Y, *et al*. Solitary breast metastasis from myxoid liposarcoma. BMC Cancer. 2014;4;14:482.
103. Morse MA, Bossen E, D'Amico TA, Williamson W, Johnson R. Myxoid liposarcoma of the supraclavicular fossa. Chest. 2000;117(5):1518-20.
104. Schwab JH, Boland P, Guo T, *et al*. Skeletal metastases in myxoid liposarcoma: an unusual pattern of distant spread. Ann Surg Oncol. 2007;14(4):1507-14.
105. Lee ATJ, Thway K, Huang PH, Jones RL. Clinical and Molecular Spectrum of Liposarcoma. J Clin Oncol. 2018;10;36(2):151-159.
106. Wei YC, Li CF, Eng HL, Yeh MC, Lin CN, Huang HY. Myxoid liposarcoma with cartilaginous differentiation: identification of the same type II TLS-CHOP fusion gene transcript in both lipogenic and chondroid components. Appl Immunohistochem Mol Morphol. 2007;15(4):477-80
107. Fritchie KJ, Goldblum JR, Tubbs RR, *et al*. The expanded histologic spectrum of myxoid liposarcoma with an emphasis on newly described patterns: implications for diagnosis on small biopsy specimens. Am J Clin Pathol. 2012;137(2):229-39.
108. Gibas Z, Miettinen M, Limon J, *et al*. Cytogenetic and immunohistochemical profile of myxoid liposarcoma. Am J Clin Pathol. 1995;103(1):20-6.
109. Scapa JV, Cloutier JM, Raghavan SS, Peters-Schulze G, Varma S, Charville GW. DDIT3 Immunohistochemistry Is a Useful Tool for the Diagnosis of Myxoid Liposarcoma. Am J Surg Pathol. 2021;1;45(2):230-239.
110. Xu S, Dong Y, Huo Z, *et al*. SOX11: a potentially useful marker in surgical pathology: a systematic analysis of SOX11 expression in epithelial and non-epithelial tumours. Histopathology. 2019;74(3):391-405.
111. Yanagida R, Balzer BL, Mckenna RJ, Fuller CB. Primary pulmonary myxoid sarcoma, a potential mimic of metastatic extraskeletal myxoid chondrosarcoma. Pathology. 2017;49(7):792-794.
112. Creytens D. Lipoblastoma-like Tumour of the Vulva, an Important Benign Mimic of Myxoid Liposarcoma. Int J Gynecol Pathol. 2019;38(2):204.
113. Mirkovic J, Fletcher CD. Lipoblastoma-like tumour of the vulva: further characterization in 8 new cases. Am J Surg Pathol. 2015;39(9):1290-5.
114. Delaney D, Diss TC, Presneau N, *et al*. GNAS1 mutations occur more commonly than previously thought in intramuscular myxoma. Mod Pathol. 2009;22(5):718-24.

115. Mrózek K, Karakousis CP, Bloomfield CD. Chromosome 12 breakpoints are cytogenetically different in benign and malignant lipogenic tumours: localization of breakpoints in lipoma to 12q15 and in myxoid liposarcoma to 12q13.3. Cancer Res. 1993;1;53(7):1670-5.
116. Potterveld S, Clay MR. Myxoid liposarcoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/softtissuemyxoidliposarcoma.html. Accessed October 8th, 2025.
117. Knight JC, Renwick PJ, Dal Cin P, Van den Berghe H, Fletcher CD. Translocation t(12;16)(q13;p11) in myxoid liposarcoma and round cell liposarcoma: molecular and cytogenetic analysis. Cancer Res. 1995;1;55(1):24-7.
118. Tirado CA, Su W, Chia V, *et al*. Patient with Myxoid/Round Cell Liposarcoma (MRCL) Involving the Well-known Translocation t(12;22): A Case Report with the Cytogenomic Landscape of this Rearrangement. J Assoc Genet Technol. 2022;48(2):68-75.