



Lipoblastomas presenting in older children and adults: analysis of 22 cases with identification of novel *PLAG1* fusion partners

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Abstract

Lipoblastomas are benign neoplasms of embryonal white fat that typically present in the first 3 years of life and show a lobular arrangement of maturing adipocytes with variable degrees of myxoid change. We systematically studied the clinicopathologic and genetic features of lipoblastomas arising in older children and adults. Cases with a diagnosis of lipoblastoma or maturing lipoblastoma in patients >3 years of age were retrieved from our archives. Immunostaining for CD34 and desmin and molecular studies (FISH, RNA sequencing) were performed. Twenty-two cases (8F; 14M) were identified in patients ranging from 4 to 44 years of age (median 10 years). Sites included extremity ($n = 15$), head and neck ($n = 4$), and trunk ($n = 3$) with tumor sizes varying from 1.6 to 17.5 cm (median 5). Only three tumors had histologic features of “conventional” lipoblastoma. The majority of tumors ($n = 14$) were composed of variably sized lobules of mature adipose tissue partitioned by thin fibrous septa (“maturing”). The remaining five cases consisted predominantly of bland spindled to plump ovoid cells embedded in a fibrous stroma, with a vaguely plexiform arrangement of small myxoid and adipocytic nodules (“fibroblastic”). CD34 was diffusely positive in all cases tested (21/21), while desmin immunoreactivity was identified in 12 of 21 cases (diffuse = 7, focal = 5). *PLAG1* rearrangements were identified in 13 tumors in the entire cohort (59%), including all 5 fibroblastic tumors. RNA sequencing detected eight *PLAG1* fusion partners, of which two were known (*CHCHD7* and *COL3A1*) and six were novel (*SRSF3*, *HNRNPC*, *PCMTD1*, *YWHAZ*, *CTDSP2*, and *PPP2R2A*). Twelve cases had follow-up (1–107 months; median 21 months), and no recurrences were reported. Lipoblastomas may occur in older children and adults and may be difficult to recognize due to their predominantly adipocytic or fibrous appearance. Awareness that lipoblastomas may occur in older patients, careful evaluation for foci showing more typical morphologic features, ancillary immunohistochemistry for CD34 and desmin, and molecular genetic studies to identify *PLAG1* rearrangements are the keys to recognizing these tumors.

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Introduction

Lipoblastomas, benign neoplasms of embryonal white fat characterized by *PLAG1* rearrangements, overwhelming affect children 3 years of age or younger [1–7]. When these tumors present in this characteristic age group they are readily recognized morphologically, consisting of a distinctly lobular, variably myxoid, highly vascular proliferation of bland, round to spindled cells and maturing adipocytes, partitioned by fibrous septa. However, as the patient ages, the adipocytic population is thought to “mature”, resulting in a well-differentiated fibro-fatty proliferation devoid of myxoid stroma, resembling an unusually septated lipoma. Consequently, lipoblastomas in older children and adults are often difficult to diagnose. Immunohistochemically, lipoblastomas are typically

CD34-positive and often show desmin expression in spindle cells, a useful diagnostic clue [8, 9]. Prompted by a recent case of lipoblastoma arising in the back of a 10-year-old male, which was composed predominantly of fibrous stroma and harbored a *CTDSP2-PLAG1* fusion, we sought to explore the pathologic and genetic spectrum of these tumors in older children and adults.

Materials and methods

The Institutional Review Boards of all participating institutions approved this study. The consultation and institutional anatomic pathology archives of Mayo Clinic were searched for cases of lipoblastoma arising in patients older than 3 years of age. All available slides were reviewed, and the cases were classified into three morphologic subtypes: conventional, maturing and fibroblastic. One additional case with fibroblastic morphology from St. Jude Children's Research Hospital was included. Clinical and follow-up data were collected from institutional medical records and the medical records of the submitting pathologists.

Immunohistochemistry

Immunohistochemistry was performed on deparaffinized, rehydrated sections obtained from a representative formalin-fixed, paraffin-embedded (FFPE) block from each case using antibody-specific epitope retrieval techniques with the Dako Envision (Dako, Carpinteria, CA, USA) automated system for detection of the following primary antigens: CD34 (Leica, QBEnd/10, 1:100) and desmin (Leica, DE-R-11, 1:50–1:100).

Fluorescence in situ hybridization

Interphase fluorescence in situ hybridization (FISH) for *PLAG1* rearrangement was performed on FFPE tumor tissues of a subset of cases using a dual-color break-apart probe set derived from bacterial artificial chromosome (BAC) clones RP11-22E14 and RP11-1130K23 as previously described [10]. In brief, RP11-22E14 mapped to the downstream (centromeric) flanking region of *PLAG1* is labeled with AF 488 FITC (green), and RP11-1130K23 targeted 5' end and the upstream sequence (telomeric) of *PLAG1* is labeled with AF555 Rhodamine (red). Prior to testing the samples accrued in this study, the FISH assay was validated in CLIA-certified laboratory at St. Jude Children's Research Hospital, and the cutoff to define *PLAG1* rearrangement was settled at 17% empirically. For each sample, 200 nuclei were analyzed, and FISH signals were scored by two experienced cytogenetic technologists independently.

RNA extraction and next-generation sequencing

FFPE tumor tissues were subjected to RNA extraction using Zymo quick-RNA FFPE kit (Zymo Research, CA). Random priming was used to synthesize cDNAs from the RNA samples extracted. For all cases except #18 and #19, an anchored multiplex PCR assay based on the Rapid Amplification of cDNA Ends (RACE) strategy followed by next-generation sequencing (Archer FusionPlex, ArcherDX, USA) was employed to identify gene fusions. We used Archer FusionPlex Sarcoma panel, which is designed to simultaneously screen for fusions of 26 genes associated with soft tissue tumors. The library of multiplex RACE products was sequenced on MiSeq (Illumina) and sequencing data were analyzed by Archer software (version 6.2). In addition to fusion detection, data from these 20 cases went through the RNA expression pipeline available with Archer v6.2 software, and *PLAG1* RNA expression was analyzed. In brief, median-normalized RNA-seq result of each case was exported in TSV format from the Archer Analysis software platform. Data for each sample were next filtered for only those amplicon locations corresponding to *PLAG1*. The median of the normalized expression values for *PLAG1* amplicons of each sample was calculated. The RNA-seq sample extracted from #18 and #19 were subjected to whole transcriptome sequencing (RNA-seq) analysis following the procedure and pipeline that have been described previously [11].

RT-PCR and Sanger Sequencing

RNA samples extracted were subjected to reverse transcription using SuperScript™ II Reverse Transcriptase (ThermoFisher Scientific, USA). Primer sequences used for PCR to verify fusions in selected cases are as follows: *CHCHD7* forward primer 5'-AAGTTGGGATGCGCGCTAC-3'; *COL3A1* forward primer 5'-CTCATGTCTGATATTTAGACATGATGAGC-3'; *HNRNPC* forward primer 5'-CAGCAGCAGTCGGCTTCTCTA-3'; *SRSF3* forward primer 5'-GTGAGAGAGTTGGTTGGTGGTGG-3'; and two reverse primers targeting *PLAG1* exons 2 and 3, respectively. *PLAG1* exon 2 reverse primer 5'-CCAAATACGGCCAAGGCAG-3' and *PLAG1* exon 3 reverse primer 5'-GAAGAGAGTGGAAATCCAATCCTTC-3'. RT-PCR products were evaluated by running agarose gel along with a 100-bp ladder DNA marker, and for *SRSF3-PLAG1* and *HNRNPC-PLAG1* fusions, bands with expected size were purified from the gel and sequenced (Sanger Sequencing).

Results

Twenty-four cases of lipoblastomas from 24 patients arising in patients >3 years of age were identified in our

institutional and consultation archives out of a total of 74 total lipoblastoma cases (32%). Two cases were excluded due to insufficient quality and quantity of the RNA extracted leaving 22 cases (8 females and 14 males) occurring in patients ranging in age from 4 to 44 years (median 10 years) (Table 1). The median ages of those with maturing, fibroblastic, and conventional morphologies were 10.5 years (range 4–44 years), 10 years (range 4–16) and 13 years (range 7–41), respectively. Sites included extremity ($n = 15$; 68%), head and neck ($n = 4$; 18%), and trunk ($n = 3$; 14%), and tumor sizes varied from 1.6 to 11.9 cm (median 5 cm).

The number of sections available per case ranged from 1 to 15 (median 3.5 sections). The majority of tumors ($n = 14$; 64%) were composed of solely of variably sized lobules of mature adipose tissue partitioned by thin fibrous septa without myxoid stroma (Fig. 1). These tumors were classified as “maturing” lipoblastoma. A smaller subset ($n = 3$; 14%) showed features of conventional lipoblastoma, with the characteristic lobules of adipocytes in various stages of maturation in a myxoid stroma with a fine capillary vascular network (Fig. 2). The remaining five cases (23%) consisted predominantly of bland spindled to plump ovoid cells embedded in a fibrous stroma with a vaguely plexiform arrangement of small myxoid and adipocytic nodules. These tumors were classified as “fibroblastic” lipoblastoma (Fig. 3). Three fibroblastic lipoblastomas showed a predominance of fibrous stroma, largely obscuring the adipocytic nature of the tumor (Fig. 4). The cells within the myxoid and fibroblastic areas displayed thin tapered nuclei without cytologic atypia or significant mitotic activity (<1 mitotic figure/10 high power fields). CD34 was diffusely positive in this population in all cases tested (21/21), while desmin immunoreactivity was identified in 12 of 21 cases (diffuse = 7, focal = 5) (Fig. 5).

PLAG1 (8q12.1) rearrangements were detected in 13 of 22 cases (59%) by RNA sequencing and/or FISH. RNA sequencing identified eight fusion partner genes across the cohort, of which two were known (*COL3A1* (2q32.2) and *CHCHD7* (8q12.1)) and six were novel. The novel partner genes, *PCMTD1* (8q11.23), *YWHAZ* (8q22.3), *CTDSP2* (12q14.1), and *PPP2R2A* (8q21.2), were found in fibroblastic tumors, whereas *SRSF3* (6p21.3-p21.1) and *HNRNPC* (14q11.2) were identified in maturing tumors. The most common fusion seen in seven lipoblastomas was *CHCHD7-PLAG1*, resulting from a cryptic intrachromosomal rearrangement at 8q12. In five lipoblastomas (four maturing and one conventional), *CHCHD7-PLAG1* was the sole fusion, whereas in two lipoblastomas (maturing), it was identified as the second *PLAG1* fusion (Table 1). All *PLAG1* fusions (except *PPP2R2A-PLAG1*) identified in this study involved the 5' untranslated regions of both *PLAG1* and a fusion partner gene. In *PPP2R2A-PLAG1*, *PPP2R2A*

(NM_002717) exon 2 fused to *PLAG1* (NM_002655) exon 3. Consequently, all fusions resulted in having the entire *PLAG1* coding sequence, which begins in exon 4, placed under the transcriptional control of promoter regions of fusion partner genes (promoter swap).

A comparison of *PLAG1* RNA expression between fusion-positive and fusion-negative groups defined by the targeted RNA-seq analysis is presented in Fig. 6, and increased expression of *PLAG1* due to promoter swap was observed in all cases except #3, #7, (borderline) and #14. The fusions transcripts revealed by targeted RNA-seq analysis in these three cases were successfully verified by RT-PCR (Supplementary Fig. 1). The relatively low expression of *PLAG1* in the three cases may be due to the low tumor content in the sample studied as these represented the maturing variant. Considering that the *SRSF3* is a novel partner to *PLAG1* fusions, the RT-PCR product of case #14 was sequenced by Sanger Sequencing, and the same fusion transcript was detected (Fig. 7). In case 5, two *PLAG1* fusions were identified, one is a known fusion (*CHCHD7-PLAG1*) and the other one showed a novel 5' partner (*HNRNPC-PLAG1*). Although high expression of *PLAG1* was observed in this case, we performed RT-PCR followed by Sanger Sequencing to verify the validity of the novel *HNRNPC-PLAG1*. Fig. 7 shows the fusion transcript detected by RT-PCR and Sanger Sequencing. Case #18 was analyzed by Whole Transcriptome Sequencing and a *PPP2R2A-PLAG1* fusion was detected; high expression of *PLAG1* was observed as well.

Clinical follow-up was available for 12 cases (1–107 months; median 21 months); no recurrences were reported.

Discussion

Lipoblastomas generally occur in children 3 years of age or younger. Approximately one-third of patients with lipoblastomas in our archives presented over the age of three; this relatively high percentage likely reflects referral bias. Although the literature contains reports of lipoblastomas arising in older children and adults, systematic reviews of the histology and genetics of these tumors beyond childhood are lacking [1–5, 7, 8, 12, 13]. Furthermore, lipoblastomas are thought to mature over time, eventually resembling ordinary lipomas or “fibrolipomas,” although evidence for this is quite scant [4, 8, 14, 15].

The results of our study suggest that lipoblastomas in older children and adults tend to follow the same anatomic site distribution as their younger counterparts, most often occurring in the extremities with a median size of 5 cm and a male predominance [1, 2, 4, 7, 16]. Although the recurrence rates in young children reach 46% in some studies, no

Table 1 Clinicopathologic characteristics of cohort.

Case	Age/ sex	Site	Morphology	CD34	Desmin	Target RNA sequencing (Archer)	FISH	Follow-up (months)
1	4/F	Hip	Maturing	P	N	No fusion identified	NP	AWOD; 78
2	4/M	Neck	Maturing	P	Fo	<i>CHCHD7-PLAG1</i>	NP	NA
3	4/M	Leg	Maturing	P	Fo	<i>CHCHD7-PLAG1</i>	NP	AWOD; 28
4	6/M	Calf	Maturing	P	P	<i>CHCHD7-PLAG1</i>	NP	AWOD; 2
5	6/M	Arm	Maturing	P	N	<i>HNRNPC-PLAG1^a</i> , <i>CHCHD7-PLAG1</i>	NP	AWOD; 25
6	6/F	Leg	Maturing	P	N	<i>CHCHD7-PLAG1</i>	NP	AWOD; 1
7	10/F	Neck	Maturing	P	P	<i>COL3A1-PLAG1^a</i> , <i>CHCHD7-PLAG1</i>	NP	AWOD; 1
8	11/F	Pretibial	Maturing	P	N	No fusion identified	NP	NA
9	18/M	Palm	Maturing	P	N	No fusion identified	NP	AWOD; 107
10	19/M	Back	Maturing	P	N	No fusion identified	NP	NA
11	29/M	Neck	Maturing	P	N	No fusion identified	NP	NA
12	31/M	Palm	Maturing	NP	NP	No fusion identified	NP	AWOD; 54
13	31/M	Thigh	Maturing	P	P	No fusion identified ^b	N	NA
14	44/F	Thigh	Maturing	P	P	<i>SRSF3-PLAG1</i>	NP	AWOD; 1
15	4/F	Neck	Fibroblastic	P	Fo	<i>PCMTD1-PLAG1</i>	NP	AWOD; 17
16	7/M	Back	Fibroblastic	P	Fo	<i>YWHAZ-PLAG1</i>	NP	NA
17	10/M	Back	Fibroblastic	P	P	<i>CTDSP2-PLAG1</i>	N	NA
18	10/F	Arm	Fibroblastic	P	P	<i>PPP2R2A-PLAG1^b</i>	N	AWOD; 5
19	16/M	Hand	Fibroblastic	P	P	No fusion identified ^{b, c}	P	NA
20	7/M	Ankle	Conventional	P	N	No fusion identified	NP	AWOD; 29
21	13/M	Arm	Conventional	P	Fo	<i>CHCHD7-PLAG1^b</i>	N	NA
22	41/F	Foot	Conventional	P	N	No fusion identified	NP	NA

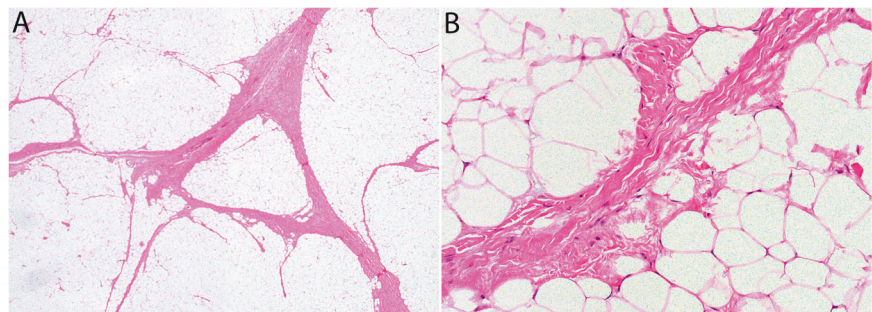
F female, M male, FISH fluorescence in situ hybridization, NP not performed, Fo focal, AWOD alive without disease, NA not available.

^aDominant fusion.

^bWhole Transcriptome Sequencing (RNA-seq) also performed.

^cThe sample for RNA-seq has a low tumor content which may impact on the test sensitivity.

Fig. 1 Maturing lipoblastomas. Lipoblastomas with maturing morphology were composed predominantly of mature adipose tissue with intervening fibrous septa (A) composed of bland spindled cells (B).



cases in our series recurred [7]. This discrepancy may be secondary to limited follow-up; alternatively, complete excision may be more feasible in older children and adults resulting in lower recurrence rates, or these lesions might simply have a lesser potential for continued growth in older children. One other explanation might be that none of our

cases had a diffuse growth pattern characteristic of lipoblastomatosis, which has a greater recurrence risk than lipoblastoma [17].

Nearly two-thirds of lipoblastomas in our cohort were composed chiefly of a lobular arrangement of mature adipose tissue with thin intervening fibrous septa, possibly

lending support to prior work suggesting that these tumors mature over time [4, 14, 18, 19]. A smaller percentage of cases harbored features of conventional lipoblastoma including myxoid lobules of adipocytes and more primitive-appearing mesenchymal cells admixed with a delicate capillary network. While we initially suspected that this conventional morphology might correlate with younger age, the median age of these patients was in fact older than in those whose tumors showed maturing histology (13 years

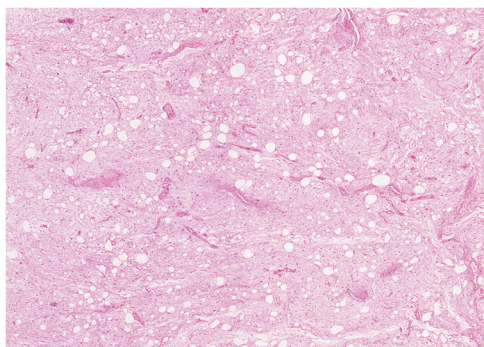


Fig. 2 Conventional lipoblastomas. Tumors with conventional morphology harbored myxoid nodules with adipocytes in varying stages of maturation and a prominent thin-walled capillary network.

Fig. 3 Lipoblastomas with fibroblastic morphology.

Fibroblastic lipoblastomas (A) harbored a plexiform arrangement of myxoid (B) and adipocytic (C) nodules set in a densely hyalinized background.

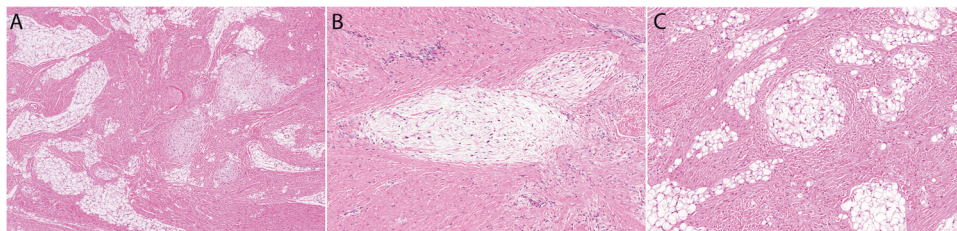


Fig. 4 Lipoblastoma with significant fibrous stroma.

Case 15 with fibroblastic morphology exhibited large amounts of fibrous stroma without myxoid or adipocytic foci (A). The spindle cell population was bland without significant atypia or mitotic activity (B, C).

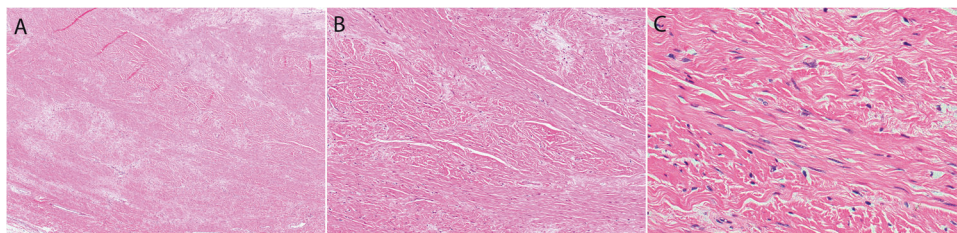
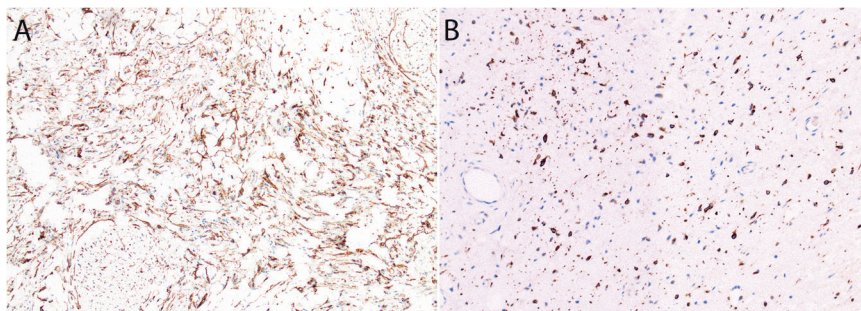


Fig. 5 Immunoprofile of lipoblastomas. Lipoblastomas showed expression of CD34 (A) and desmin (B).



vs. 10.5 years). The remaining five cases in our series were predominantly fibroblastic, composed of small adipocytic and myxoid nodules embedded in a dense collagenous background, with a vaguely plexiform low-power appearance. While there are occasional reports of this unusual variant, lipoblastomas with this morphology are likely rare, under recognized or both [20, 21]. The spindle cell component of the fibroblastic variant, similar to those with conventional and maturing histologies, co-expressed CD34 and desmin [8, 9, 22].

The genetic hallmark of lipoblastoma is chromosomal translocations resulting in *PLAG1* rearrangement and its subsequent upregulation as a result of promoter swapping [23–29]. To date, various fusion partners of *PLAG1* have been reported including *COL1A2* (7q21.3), *HAS2* (8q24.13), *RAD51B* (14q24.1), *COL3A1* (2q32.2), *RAB2A* (8q12.1-q12.2), and *BOC* (3q13.2) [28, 30–35]. Approximately 60% of cases in our group showed *PLAG1* rearrangement, similar to the rates reported in the literature [36, 37]. Although the *PLAG1* negative cases tended to occur in older patients for each subtype, these cases were reviewed by two soft tissue pathologists and felt to represent lipoblastomas. *CHCHD7* represented the most common fusion partner in our series. *CHCHD7-PLAG1* fusions,

also resulting in promotor swap and activation of *PLAG1*, have been reported as recurrent events in pleomorphic adenomas of the salivary gland, but not described previously in lipoblastoma [38–41].

We identified six novel fusions including *HNRNPC-PLAG1*, *SRSF3-PLAG1*, *PCMTD1-PLAG1*, *YWHAZ-PLAG1*, *CTDSP2-PLAG1*, and *PPP2R2A-PLAG1*. These novel fusion partners revealed in this study may help to elucidate molecular genetic alterations of some previously reported cytogenetic abnormalities in lipoblastomas. For instance, McVay et al. reported a case with an inv (p21.3q11.23) [42]. As *PPP2R2A* is located at 8p21.3, the inv [8] in this case may produce a *PPP2R2A-PLAG1* fusion. Another example is a case with t(6;8)(p21;q12) reported by Coffin et al. [7]. This chromosome translocation

could result in a *SRSF3-PLAG1* fusion as *SRSF3* is located at 6p21.31-p21.2. The novel fusions all were identified in the non-conventional lipoblastomas in our cohort (four fibroblastic and two maturing).

In three cases, *PLAG1* rearrangements identified by RNA sequencing were undetected by FISH studies. *CHCHD7* and *PLAG1* are neighbor genes only a few hundred base pairs apart at 8q12.1 and are transcribed in opposite directions. The FISH probes derived from BAC clones are not capable to detect this extremely cryptic fusion. Interestingly, the FISH assay failed to detect the other two fusions, *CTDSP2-PLAG1* and *PPP2R2A-PLAG1*. *CTDSP2* and *PPP2R2A* are located at 12q13 and 8p21, respectively. The discrepancy between RNA sequencing analysis and the current FISH study may suggest that cryptic chromosomal rearrangements are common in *PLAG1* fusions and these fusions may be overlooked if high-resolution sequencing is not performed.

The differential diagnosis of lipoblastomas in older children and adults depends on the morphologic subtype. “Maturing” lipoblastomas are most likely to mimic atypical lipomatous tumor/well-differentiated liposarcomas. Careful examination of the fibrous septa for the atypical hyperchromatic stromal cells present in the latter in conjunction with FISH studies for *MDM2* amplification should aid in appropriate classification. Outside of infancy, the conventional variant of lipoblastoma must be differentiated from myxoid liposarcoma, the most common form of pediatric liposarcoma [43]. Although lipoblastomas typically show more prominent lobulation, display maturation toward the periphery of lobules, and lack “myxoid pools”, molecular genetic studies for *DDIT3* and/or *PLAG1* may be necessary for definitive classification. The fibroblastic variant may simulate other entities with a plexiform growth pattern such as cellular neurothekeoma and plexiform fibrohistiocytic tumor. The

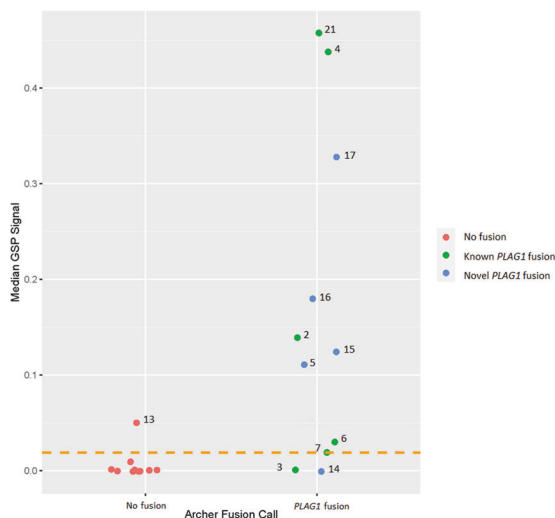
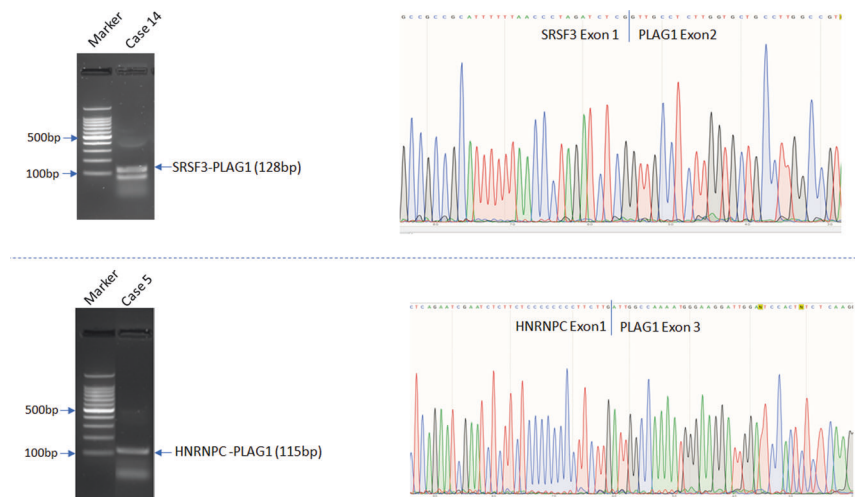


Fig. 6 *PLAG1* RNA expression. Comparison of *PLAG1* RNA expression between fusion-positive and fusion-negative groups defined by the targeted RNA-seq analysis. The median of the normalized expression values for *PLAG1* amplicons of each sample is presented.

Fig. 7 Molecular confirmation of fusions. RT-PCR and Sanger Sequencing confirmation of *SRSF3-PLAG1* fusion in case #14 and *HNRNPC-PLAG1* fusion in case #5. Upper panel: *SRSF3-PLAG1* fusion transcript was verified by RT-PCR using *SRSF3* forward and *PLAG1* exon 2 reverse primers. Sequencing of the band at 128 bp confirmed the fusion. Lower panel: *HNRNPC-PLAG1* fusion transcript was verified by RT-PCR using *HNRNPC* forward and *PLAG1* exon 3 reverse primers. Sequencing of the band at 115 bp confirmed the fusion.



former may show myxoid change but lacks the adipocytic component present in lipoblastoma, while plexiform fibrohistiocytic tumors show giant cell and histiocyte-rich nodules without myxoid stroma. Tumors with a predominance of fibroblastic stroma may also raise the possibility of low-grade fibromyxoid sarcoma, a tumor which can be excluded by MUC4 immunohistochemistry. Finally, fibrous hamartoma of infancy usually occurs within the first 2 years of life and shows a distinct triphasic appearance of bland fibroblasts/myofibroblasts, primitive-appearing spindle cells, and mature fat.

In summary, we have reported the largest series of lipoblastomas arising in patients older than 3 years of age, with characterization of their immunohistochemical and genetic features, including seven novel fusions not previously identified in lipoblastomas. As lipoblastomas in this population may harbor fibroblastic areas, careful examination for adipocytic or myxoid stroma in conjunction with CD34/desmin immunostains and *PLAG1* molecular studies should aid in appropriate diagnosis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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