Recurrent Fusion of the GRB2 Associated Binding Protein 1 (GAB1) Gene With ABL Proto-oncogene 1 (ABL1) in Benign Pediatric Soft Tissue Tumors

IOANNIS PANAGOPOULOS1, LUDMILA GORUNOVA1, KRISTIN ANDERSEN1, SVETLANA TAFJORD2, MARIUS LUND-IVERSEN2, INGVILD LOBMAIER2, FRANCESCA MICCI1 and SVERRE HEIM1,3

1Section for Cancer Cytogenetics, Institute for Cancer Genetics and Informatics, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway;
2Department of Pathology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway;
3Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Abstract. Background/Aim: Fusions of the ABL proto-oncogene 1 gene (ABL1 in 9q34) are common in leukemias but rare in solid tumors. The most notable is the t(9;22)(q34;q11)/BCR-ABL1 coding for a chimeric tyrosine kinase. We herein report an ABL1-fusion in a pediatric tumor. Materials and Methods: G-banding, fluorescence in situ hybridization, reverse transcription polymerase chain reaction and Sanger sequencing were performed on a soft tissue perineurioma found in the left musculus erector spinae of a child. Results: A der(4)t(4;9)(q31;q34) and a fusion of the GAB2 associated binding protein 1 (GAB1 in 4q31) gene with ABL1 were found. A literature search revealed 3 more cases with similar genetic and clinicopathological characteristics: a soft tissue perineurioma with t(2;9;4)(p23;q34;q31) and ABL1 rearrangement, a soft tissue angiofibroma with a GAB1-ABL1 chimeric gene, and a solitary fibrous tumour carrying a der(4)t(4;9)(q31.1;q34). Conclusion: GAB1-ABL1 is a recurrent fusion gene in benign pediatric tumors.

The ABL proto-oncogene 1 gene (ABL1, previous symbol ABL) in chromosome band 9q34 is ubiquitously expressed and codes for a non-receptor tyrosine kinase which is localized at many subcellular sites including the nucleus, cytoplasm, mitochondria, and endoplasmic reticulum. It is involved in a variety of cellular processes such as cell division, adhesion, differentiation, and response to stress (1-3). ABL1 together with ABL2 (the proto-oncogene 2 gene which encodes a non-receptor tyrosine kinase and maps to chromosome band 1q25) constitute the ABL family of kinase genes (2, 4-6). Both ABL1 and ABL2 fuse with a variety of translocation partner genes in various hematological malignancies (7-10). The most notable fusion is between ABL1 and the 5' end of the breakpoint cluster region gene (BCR), located in 22q11, through the t(9;22)(q34;q11) chromosome translocation that gives rise to the Philadelphia chromosome in chronic myeloid leukemia (CML) (11, 12). The BCR-ABL1 fusion gene codes for a leukemogenic, constitutively active tyrosine kinase (11, 12). The discovery that 2-phenylaminopyrimidines inhibit the ABL protein kinase both in vitro and in vivo, led to the development of imatinib mesylate that now constitutes the first-line treatment of CML, as well as to introduction of other protein kinase inhibitors into cancer therapy (13-19).

Rearrangements of the ABL1 and ABL2 genes in solid tumors have also been documented (3-6, 20). Phosphorylation and activation of ABL kinases were reported in various tumors such as breast and lung adenocarcinomas, melanomas, and cancers of the brain (3-6, 20). The mechanisms for activation of ABL1 and ABL2 kinases are in these settings not chromosome translocations/fusion genes but rather genomic amplification, increased expression of mRNA, enhanced protein expression, and increased catalytic activity (3-6, 20).

Perineurioma is a tumor composed entirely of neoplastic perineurial cells with ultrastructural and immunohistochemical features similar to those of their normal counterparts (21). According to the latest WHO Tumors of Soft Tissue and Bones, perineuriomas are nearly always benign, although rare malignant variants have been reported (22). There are two
main types: intraneural perineuriomas are confined within peripheral nerve boundaries whereas extraneural perineuriomas are found in soft tissue and skin (21, 23-25). Based on clinicopathological characteristics, the extraneural tumors are further subdivided into soft tissue, sclerosing, and reticular lesions (21, 23, 26-33).

In the present study, we report the finding of fusion of the GRB2 associated binding protein 1 (GAB1) gene with ABL1 in a pediatric soft tissue perineurioma. We review the literature and conclude that GAB1-ABL1 is a recurrent fusion which appears to characterize a benign, pediatric tumor type.

Materials and Methods

Ethics statement. The study was approved by the Regional Ethics Committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norge, http://helseforskning.etikkom.no; 2010/1389/REK sør-ost A). Written informed consent was obtained from the patient’s parents. The Ethics Committee’s approval included a review of the consent procedure. All patient information has been de-identified.

Case description. The patient was a 12-year-old boy with a tumor in the left erector spinae musculature. It measured 65×45×20 mm, was circumscribed but unencapsulated, and showed small areas of infiltration into the skeletal muscle. Microscopically, a whorled to storiform growth pattern was seen (Figure 1). The tumor cells were relatively uniform with oval, slender, relatively uniform nuclei. The cytoplasm showed elongated extensions within a collagenous stroma. Mitotic figures were rarely seen. Immunohistochemistry performed at the primary lab showed negative results for epithelial membrane antigen (EMA), S100 protein, mucin 4 (MUC4), and cluster of differentiation 34 (CD34). After consulting Professor Jason Hornick, Department of Pathology, Brigham and Women’s Hospital, Boston, USA, the patient was diagnosed as having a soft tissue perineurioma. Repeated EMA immunohistochemistry at Brigham & Women’s Hospital was focally positive.

G-Banding, karyotyping, and fluorescence in situ hybridization (FISH). Cells from a representative area of the tumor were short-term cultured and analyzed cytogenetically as previously described (34). The karyotype was written according to the International System for Human Cytogenomic Nomenclature (35). FISH experiments were performed on interphase nuclei using the ZytoLight SPEC ABL1 Dual

Figure 1. Hematoxylin and eosin (H&E) staining of a pediatric soft tissue perineurioma. A) H&E stained section showing well demarcated, unencapsulated, highly cellular solid tumor tissue, magnification 1x. B) H&E stained section (low magnification) showing ovoid to spindle cells, magnification 4x. C) H&E-stained section showing a whorled to storiform growth pattern, magnification 10x. D) H&E-stained section showing relatively uniform cells with oval-shaped to slender, tapering nuclei, magnification 20x.
Color Break Apart Probe (ZytoVision, Bremerhaven, Germany) following the company’s recommendations.

Reverse transcription (RT) polymerase chain reaction (PCR) and Sanger sequencing. Total RNA was extracted from frozen (-80°C) tumor tissue adjacent to that used for cytogenetic analysis and histological examination using miRNeasy Mini Kit (Qiagen, Hilden, Germany). For cDNA synthesis, the iScript Advanced cDNA Synthesis Kit for RT-qPCR was used to reverse transcribe one µg of total RNA according to the manufacturer’s instructions (Bio-Rad, Hercules, CA, USA). cDNA corresponding to 20 ng total RNA was used as template in subsequent PCR assays. The BigDye Direct Cycle Sequencing Kit was used for PCR/cycle (Sanger) sequencing according to the company’s recommendations (ThermoFisher Scientific, Waltham, MA, USA). The primers were M13For-GAB1-1676F1: TGTAAAACGACGGCCAGTCCACCACGACAACATTCCAGCAGTT and M13Rev-ABL1-167R1: CAGGAAACAGCTATGACCGGTCATTTTCACTGGGTCCAGCGA. Sequencing was run on the Applied Biosystems SeqStudio Genetic Analyzer system (ThermoFisher Scientific). For computer analysis of sequence data, the basic local alignment search tool (BLAST) software (https://blast.ncbi.nlm.nih.gov/Blast.cgi) was used (36). The web version of Open Reading Frame Finder at NCBI (https://www.ncbi.nlm.nih.gov/orffinder/) was used to search for open reading frames of the sequence.

Results

The initial G-banding analysis yielded a karyotype with a three-way chromosomal translocation as the only cytogenetic aberration: 46,XY,t(1;9;4)(p34~35;q34;q31)[7]/46,XY[4] (Figure 2). FISH with the ZytoLight SPEC ABL1 Dual Color Break Apart Probe showed the following signal pattern in 92 out of 246 (37%) examined interphase nuclei: one red/green (corresponding to normal ABL1), one red (distal part of the probe), and two green signals (proximal part of the probe) (Figure 3A). The results indicated rearrangements of both ABL1 and the region immediately proximal to this gene which hybridized to the 710 Kbp green-labelled part of the probe (Figure 3B). Taking into consideration the initial karyotype as well as the FISH results, we concluded that the observed rearrangement was more complex than it appeared and included at least one cryptic change. A likely explanation is that two cytogenetic events had taken place (Figure 3C): a translocation between chromosomes 4 and 9 which generated a der(4)t(4;9)(q31;q34) and a der(9)t(4;9)(q31;q34), and a translocation between chromosomes 1 (p34~35) and the der(9)t(4;9)(q31;q34). The breakpoint on the der(9) occurred just upstream (proximal) of the ABL1 gene (Figure 3B and C). Thus, part of 9q34 together with 4q31-qter material is translocated to the der(1). Further, the segment from 1pter to 1p34~35 is translocated onto 9q34 from the der(9)t(4;9)(q31;q34) (Figure 3C) which is why we observed two green signals by interphase FISH; a part of the “green” region of the probe hybridized to der(1) whereas the other part hybridized to der(9) (Figure 3C). If we therefore reassess the G-banding karyotype in light of the FISH data, we arrive at the following karyotype: 46,XY,der(1)(4qter-
PCR/cycle (Sanger) sequencing with the primer combination M13For-GAB1-1676F1 and M13Rev-ABL1-167R1 revealed a fusion of \textit{GAB1} exon 6 (nucleotide 1898 in the reference sequence NM_002039.4) with \textit{ABL1} exon 2 (nucleotide 83 in the reference sequence NM_005157.4) (Figure 4A). Based on the fusion point detected and the reference sequences

Figure 3. FISH analyses of a pediatric soft tissue perineurioma. A) FISH with the ABL1 break apart probe on a normal nucleus and a nucleus with aberrant hybridization pattern suggesting rearrangements of both ABL1 and the region proximal to ABL1. B) A diagram of the Zytolight ABL1 break apart probe. Vertical arrows indicate the rearranged regions. C) Diagram showing two hypothetical cytogenetic events that would explain the observed FISH results: Left, translocation between chromosomes 4 and 9 generating the derivative chromosomes der(4)t(4;9)(q31;q34) and der(9)t(4;9)(q31;q34); right, translocation between chromosomes 1 (p34~35) and der(9)t(4;9)(q31;q34) which gives rise to der(1)(4qter->4q31::9q34->9q34::1p34~35->qter) and der(9)t(1;9)(p34~35;q34). The chromosomes are not in scale.
NM_002039.4 and NM_005157.4, the GAB1-AB1 fusion transcript is in frame and coding for a 1632 amino acid residues (aa) protein in which the first 528 aa come from GAB1 while the other 1104 aa are from ABL1 (Figure 4B).

**Discussion**

We herein present a soft tissue perineurioma with a der(4)t(4;9)(q31;q34) which gave rise to a GAB1-AB1...
fusional fibrous tumor. A search of the literature revealed 3 additional cases with similar genetic and clinicopathologic characteristics (Table I, cases 9, 11, and 12).

The first tumor was found in the right shoulder of a 9-year-old girl (Table I, case 11). It was diagnosed as a benign solitary fibrous tumor (SFT). Among various chromosome aberrations, also a der(4)(q31.1;q34) was found (37). SFT may mimic other tumors, among them soft tissue perineurioma (21, 23, 33, 38, 39). However, SFTs are characterized by the pathognomonic NAB2-STAT6 fusion gene resulting from an intrachromosomal inversion involving 12q13.3, which leads to nuclear expression of STAT6 (38-44). Thus, “One should be cautious to call an “SFT-like” tumor an SFT without a positive STAT6 immunostain result” (44).

The second tumor was found in the forearm of a 14-year-old girl (Table I, case 9). It was diagnosed as a soft tissue perineurioma and had a t(2;9;q34) chromosome translocation as the sole cytogenetic aberration (45). Additional experiments with array-comparative genome hybridization and FISH showed that the three-way translocation resulted in interstitial deletions in 2p and 9q as well as rearrangement of ABL1. The 5’ part of ABL1 was deleted whereas the 3’ part was moved to the der(4) (45). The authors concluded that “the translocation between the distal end of the 9q deletion, which is located at 9q34.12, and 4q31 could very likely be significant because 3’ ABL1 is involved” (45). Because the tumor we examined displayed a similar cytogenetic pattern to that of the above-mentioned tumors, i.e., the initial karyotype showed a three-way translocation with breakpoints in chromosome bands 4q31 and 9q34, we performed FISH with an ABL1 break apart probe. This showed splitting of ABL1 (Figure 3A). We considered the possibility that an ABL1-fusion might be located on the der(4), and therefore searched the relevant literature for ABL1 fusions in mesenchymal tumors. This gave information on a third tumor which was located in the foot of a 7-year-old boy, diagnosed as a soft tissue angiofibroma and carrying a GAB1-ABL1 fusion gene (46) (Table I, case 12). However, soft tissue angiofibromas are characterized by the pathognomonic t(5;8)(p15;q13) chromosome translocation or variants thereof resulting in an ABL1-ABL1 fusion gene (46-50). Moreover, in a case of soft tissue angiofibroma (51), a t(7;8;14)(q11;q13;q31) translocation was found resulting in a GTF2I-NCAM1 fusion. This further emphasizes the role of NCAM1-rearrangements in the development of soft tissue angiofibroma (51). Because there are histologic and immunohistochemical similarities between soft tissue angiofibroma and soft tissue perineurioma (21, 23, 48, 49, 52-55) and because GAB1 maps on chromosome band 4q31, we investigated the present tumor to see if a GAB1-ABL1 fusion gene had been generated. Using RT-PCR/cycle (Sanger) sequencing, we detected an in-frame GAB1-ABL1 fusion transcript with the fusion point identical to the one previously described (46). Because both the GAB1 and ABL1 genes on 4q31 and 9q34, respectively, are transcribed from centromere to telomere, the GAB1-ABL1 fusion gene is predicted to be formed on der(4). Thus, we conclude that the tumor with

### Table I. Clinicopathological data on published intraneural, sclerosing, and soft tissue perineuriomas with abnormal karyotypes. The solitary fibrous tumor with der(4)(q31.1;q34) and the soft tissue angiofibroma with GAB1-ABL1 and associated (assumed) t(4;9) are included.

| Case | Morphology       | Gender/Age | Location         | Karyotype                                                                 | Reference |
|------|------------------|------------|------------------|---------------------------------------------------------------------------|-----------|
| 1    | Intraneural      | F/38       | Posterior        | 45,XX,add(14)(p13)-22,add(22)(q11)                                        | (59)      |
| 2    | Intraneural      | F/11       | Elbow            | 46,XX,add(2)(q11.2),add(3)(q12)                                           | (61)      |
| 3    | Sclerosing       | M/7        | Finger           | 46,XY,t(2;10)(p23;q24),der(10)(t(2;10)(t(10;10)(p52;q24)                     | (61)      |
| 4    | Sclerosing       | F/15       | Finger           | 47,XX,add(3)(q23),add(6)(1q21),-5,-9,-10,-22,+mar1,+mar2,+mar3           | (60, 67) |
| 5    | Sclerosing       | F/15       | Finger           | 46,XX,-10,del(10)(q22q24),+mar(26)/47,XX,-10,del(10)(q22q24)+mar,x2/12/46,XX | (62)      |
| 6    | Soft tissue      | F/26       | Thigh            | 45,XX,-13/45,XX,der(13;14)(q10;q10)                                       | (63)      |
| 7    | Soft tissue      | F/13       | Intraabdominal   | 46,XX,t(8;9)(q13;q22)                                                    | (61)      |
| 8    | Soft tissue      | M/43       | Foot             | 46,XY,add(2)(q33),t(4;10)(q25;q24)[10]/45,iderm,                         | (65)      |
| 9    | Soft tissue      | F/14       | Forearm          | 46,XX,t(2;9;4)(p23;q34)                                                   | (45)      |
| 10   | Soft tissue      | M/12       | Erector          | 46,XY,der(1)(4qter>4q31:9q43>9q34:1p34-35>1qter),der(4)t(4;9)(q31;q34),del(9q34),der(9q34),ins(9q34) | Present    |
| 11   | Solitary         | F/9        | Shoulder         | 46,XX,der(4)(t(4;9)(q31.1;q34),del(9q)(p22q24),                       | (37)      |
| 12   | Soft tissue      | M/7        | Foot             | GAB1-ABL1 fusion gene/t(4;9)(q31;q34)                                    | (46)      |
der(4)t(4:9)(q31.1;q34) (37) and the one with t(2;9;4) (p23;q34;q31) (45) both carried a GAB1-ABL1 fusion gene. In fact, a simple, balanced t(4;9)(q31;q34) chromosome translocation could generate a GAB1-ABL1 fusion.

The GAB1-ABL1 fusion gene would code for a chimeric protein in which the first 28 aa of ABL1 are replaced by the first 528 aa of GAB1. It retains the pleckstrin homology (PH) domain of GAB1 and all the functional domains of ABL1, including the kinase domain (2, 9, 56-58). Thus, GAB1-ABL1 is predicted to be a chimeric tyrosine kinase with similar functions to the chimeric kinases BCR-ABL1, ETV6-ABL1, NUP214-ABL1, ZMIZ1-ABL1, and EML1-ABL1 which were found in hematologic malignancies (9).

Only a limited number of perineuriomas have been studied genetically. Karyotypic data exist on two intraneural tumors, three sclerosing tumors, and, including the present case, five soft tissue perineuriomas (Table I) (45, 59-63). Molecular genetic studies, including FISH, are also very few (28, 60, 64-66).

In intraneural perineurioma, a deletion in chromosome band 22q11 was reported in the first tumor examined whereas structural aberrations of 2q11 and 3q12 were seen in the second (59, 61) (Table I, cases 1 and 2). Whole-exome sequencing and copy number variation analysis of another 16 intraneural perineuriomas detected mutation in the TRAF7 gene (which maps on 16p13) in 10 (60%) and larger deletions of chromosomes 10, 11, and 22 in two tumors (65).

In the three reported sclerosing perineuriomas with abnormal karyotypes, alteration of chromosome 10 was seen (60, 61) (Table I, cases 3, 4, and 5). One tumor had two chromosome translocations involving 10q24 (Table I, case 3), a second had loss of chromosomes 10 and 22 (Table I, case 4), and the third had a deletion involving 10q24 and loss of chromosome 10 (Table I, case 5) (60, 61, 67). Molecular studies of sclerosing tumors suggested a tumorigenic role of NF2 (on 22q12.2) abnormalities (60, 64). Lasota et al. (64) found point mutations in NF2 coding sequences in three of five sclerosing perineuriomas while Sciot et al. (60) found a cryptic deletion in NF2, in addition to a deletion involving 10q24, in another sclerosing perineurioma (Table I, case 5).

In soft tissue perineuriomas other than the above-mentioned tumors, three more cases have been reported with abnormal karyotypes (Table I, cases 6, 7, and 8): a tumor of the thigh in a 26-year-old woman showing loss of chromosome 13 (Table I, case 6), an intrabdominal tumor in a 13-year-old girl with a t(8;9)(q13;q22) as the sole cytogenetic aberration (Table I, case 7), and a tumor of the foot in a 43-year-old man whose tumor cells had an add(2)(q33) and t(4;10)(q25;q24) (Table I, case 8) (61-63). Whole exome sequencing and copy number variation analysis of 14 soft tissue perineuriomas showed deletions of 22q12 encompassing NF2 in 6 tumors, whereas 4 tumors had deletion of 17q11 encompassing NF1. No point mutations were detected in NF1, NF2, or TRAF7 (66).

The existing data, those previously published together with what we describe here, therefore indicate three different pathogenetic pathways in perineuriomas. The first pathway involves rearrangements of chromosome 22/NF2 gene or chromosome 17/NF1 gene, the second involves chromosome band 10q24, whereas the third involves chromosome translocations in which chromosome bands 4q31 and 9q34 are recombined to generate a GAB1-ABL1 fusion gene.

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest in regard to this study.

Authors’ Contributions

IP designed and supervised the research, performed molecular genetic experiments and bioinformatics analysis, and wrote the article. LG performed cytogenetic analysis and evaluated the FISH data. KA performed molecular genetic experiments, FISH analyses, and evaluated the data. ST performed pathological examination. ML-I performed pathological examination. FM evaluated the cytogenetic and FISH data. SH assisted with experimental design and writing of the article. All Authors read and approved the final manuscript.

Acknowledgements

The Authors thank Professor Jason Hornick, Department of Pathology, Brigham and Women’s Hospital, Boston USA for help with the diagnosis. This work was supported by grants from Radiumhospitalets Legater.

References

1 Colicelli J: ABL tyrosine kinases: Evolution of function, regulation, and specificity. Sci Signal 3(139): re6, 2010. PMID: 20841568. DOI: 10.1126/scisignal.3139re6
2 Wang JY: The capable ABL: What is its biological function? Mol Cell Biol 34(7): 1188-1197, 2014. PMID: 24421390. DOI: 10.1128/MCB.01454-13
3 Khatri A, Wang J and Pendergast AM: Multifunctional ABL kinases in health and disease. J Cell Sci 129(1): 9-16, 2016. PMID: 26729027. DOI: 10.1242/jcs.175521
4 Greuber EK, Smith-Pearson P, Wang J and Pendergast AM: Role of ABL family kinases in cancer: From leukemia to solid tumours. Nat Rev Cancer 13(8): 559-571, 2013. PMID: 23842646. DOI: 10.1038/nrc3563
5 Wang J and Pendergast AM: The emerging role of ABL kinases in solid tumors. Trends Cancer 1(2): 110-123, 2015. PMID: 26645050. DOI: 10.1016/j.trecan.2015.07.004
6 Tripathi R, Liu Z and Platffner R: Enabling tumor growth and progression: Recent progress in unraveling the functions of ABL kinases in solid tumor cells. Curr Pharmcol Rep 4(5): 367-379, 2018. PMID: 30746323. DOI: 10.1007/s40495-018-0149-y
20 Ganguly SS and Plattner R: Activation of ABL family kinases
21 Macarenco RS, Ellinger F and Oliveira AM: Perineurioma: A
distinctive and underrecognized peripheral nerve sheath
neoplasm. Arch Pathol Lab Med 131(4): 625-636, 2007. PMID:
17425397. DOI: 10.1045/1543-2165(2007)131[625:PADAUP]2

22 Hornick JL, Fletcher CDM and Fletcher JA: Perineurioma. In:
World health organization classification of tumours of soft tissue
and bone. Fletcher CDM, Bridge JA, Hogendoorn PCW and
Mertens F (eds.). IARC Press: Lyon, pp. 176-178, 2013.
23 Hornick JL and Fletcher CD: Soft tissue perineurioma:
Clinicopathologic analysis of 81 cases including those with
atypical histologic features. Am J Surg Pathol 29(7): 845-858,
2005. PMID: 15958848. DOI: 10.1097/01.pas.0000155166.86409.d2
24 Boyanton BL Jr, Jones JK, Shenaq SM, Hicks MJ and
Bhattacharjee MB: Intraneural perineurioma: A systematic
review with illustrative cases. Arch Pathol Lab Med 131(9):
1382-1392, 2007. PMID: 17824794. DOI: 10.1043/1543-
2165(2007)131[1382:IPASRW]2.0.CO;2
25 Mauermann ML, Amrami KK, Kuntz NL, Spinner RJ, Dyck PJ,
Bosch EP, Engelstad J, Felmlee JP and Dyck PJ: Longitudinal
study of intraneural perineurioma—a benign, focal hypertrophic
neuropathy of youth. Brain 122(Pt 8): 2265-2276, 2009. PMID:
19567701. DOI: 10.1093/brain/awp169
26 Tsang WY, Chan JK, Chow LT and Tse CC: Perineurioma: An
uncommon soft tissue neoplasm distinct from localized benign
hypertrophic neuropathy and neurofibroma. Am J Surg Pathol
16(8): 756-763, 1992. PMID: 1497116. DOI: 10.1097/00000478-
1997208000-00003
27 Fetsch JF and Miettinen M: Sclerosing perineurioma: A
clinicopathologic study of 19 cases of a distinctive soft tissue
lesion with a predilection for the fingers and palms of young
adults. Am J Surg Pathol 21(12): 1433-1442, 1997. PMID:
9414186. DOI: 10.1097/00000478-1997122000-00005
28 Giannini C, Scheithauer BW, Jenkins RB, Erlandson RA, Perry
A, Borell TJ, Hoda RS and Woodruff JM: Soft-tissue
perineurioma. Evidence for an abnormality of chromosome 22,
criteria for diagnosis, and review of the literature. Am J Surg
Pathol 21(2): 164-173, 1997. PMID: 9042282. DOI:
10.1097/00000478-1997072000-00005
29 Graadt van Roggen JF, McMenamin ME, Belchis DA, Nielsen GP,
Rosenberg AE and Fletcher CD: Reticular perineurioma: A
distinctive variant of soft tissue perineurioma. Am J Surg Pathol
25(4): 485-493, 2001. PMID: 11257623. DOI: 10.1097/00000478-
200104000-00008
30 Balarazeo FS, Muller RC, Weiss RG, Brown T, Knibbs D and
Joshi VV: Soft tissue perineuriomas in children: Report of three
cases and review of the literature [corrected]. Pediatr Dev Pathol
6(2): 137-141, 2003. PMID: 12545720. DOI: 10.1055/s-10024-
0119-x
31 Canales-Ibarra C, Magarinos G, Olsoff-Pagovich P and Ortiz-
Hidalgo C: Cutaneous sclerosing perineurioma of the digits: An
uncommon soft-tissue neoplasm. Report of two cases with
immunohistochemical analysis. J Cutan Pathol 30(9): 577-581,
2003. PMID: 14507408. DOI: 10.1043/j.1600-0560.2003.00108.x
32 Yamaguchi U, Hasegawa T, Hirose T, Fugo K, Mitsuhashi T,
Shimizu M, Kawai A, Ito Y, Chuman H and Beppu Y: Sclerosing
perineurioma: A clinicopathologic study of five cases and
diagnostic utility of immunohistochemical staining for glut1.
Virchows Arch 443(2): 159-163, 2003. PMID: 12836021. DOI:
10.1007/s00428-003-0849-4
33 Rankine AJ, Filion PR, Platten MA and Spagnolo DV:
Perineurioma: A clinicopathological study of eight cases.
Pathology 36(4): 309-315, 2004. PMID: 15370128. DOI:
10.1080/031302041001721663
Panagopoulos et al: GAB1-ABL1 Fusion Gene in Soft Tissue Perineurioma

34 Panagopoulos I, Gorounova L, Lund-Iversen M, Andersen K, Andersen HK, Lobmaier I, Bjerkhagen B and Heim S: Cytogenetics of spindle cell/pleomorphic lipomas: Karyotyping and fish analysis of 31 tumors. Cancer Genomics Proteomics 15(3): 193-200, 2018. PMID: 29695401. DOI: 10.21873/cgp.20077

35 McGowan-Jordan J, Simons A and Schmid M: ISCN 2016: An international system for human cytogenomic nomenclature Karger: Basel, pp. 140, 2016.

36 Altschul SF, Gish W, Miller W, Myers EW and Lipman DJ: Basic local alignment search tool. J Mol Biol 215(3): 403-410, 1990. PMID: 2231712. DOI: 10.1016/S0022-2836(05)80360-2

37 Rakheja D, Wilson KS, Meehan JJ, Schultz RA, Maale GE and Timmons CF: Extrapleural benign solitary fibrous tumor in the shoulder of a 9-year-old girl: Case report and review of the literature. Pediatr Dev Pathol 7(6): 653-660, 2004. PMID: 15630539. DOI: 10.1016/s1002-044-6065-7

38 Doyle LA, Vivero M, Fletcher CD, Mertens F and Hornick JL: Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mod Pathol 27(3): 390-395, 2014. PMID: 24030747. DOI: 10.1038/modpathol.2013.164

39 Vogels RJ, Vlenterie M, Versele-Jonkers YM, Ruijter E, Bekers EM, Verdijk MA, Link MM, Bonenkamp JJ, van der Graaf WT, Slootweg PJ, Suurmeijer AJ, Groenen PJ and Flucke U: Solitary fibrous tumor - clinicopathologic, immunohistochemical and molecular analysis of 28 cases. Diagn Pathol 9: 224, 2014. PMID: 25432794. DOI: 10.1186/s13004-014-0224-6

40 Chmielecki J, Crago AM, Rosenberg M, O'Connor R, Walker SR, Ambrogio L, Auclair D, McKenna A, Heinrich MC, Frank DA and Meyerson M: Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet 45(2): 131-132, 2013. PMID: 23313954. DOI: 10.1038/ng.2522

41 Mohajeri A, Tayebwa J, Collin A, Nilsson J, Magnusson L, van Steyven FV, Brosoj O, Domanski HA, Larsson O, Sciot R, Debic-Rychter M, Hornick JL, Mandahl N, Nord KH and Mertens F: Comprehensive genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, nonrandom secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. Genes Chromosomes Cancer 52(10): 873-886, 2013. PMID: 23225380. DOI: 10.1002/gcc.22033

42 Robinson DR, Wu YM, Kalyana-Sundaram S, Cao X, Longiro RJ, Sung YS, Chen CL, Zhang L, Wang R, Su F, Iyer MK, Roychowdhury S, Siddiqui J, Pienta KJ, Kunju LP, Mertens F, Domanski HA, Larsson O, Sciot R, Debic-Rychter M, Hornick JL, Mandahl N, Nord KH and Mertens F: Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 45(2): 180-185, 2013. PMID: 23313952. DOI: 10.1038/ng.2509

43 Demico EG, Harms PW, Patel RM, Smith SC, Ingrain D, Torres K, Carskadon SL, Camelo-Piragua S, McHugh JB, Siddiqui J, Palanisamy N, Lucas DR, Lazar AJ and Wang WL: Extensive survey of STAT6 expression in a large series of mesenchymal tumors. Am J Clin Pathol 143(5): 672-682, 2015. PMID: 25873501. DOI: 10.10130/AICPN25NJTOUNPNF

44 Wei S, Henderson-Jackson E, Qian X and Bui MM: Soft tissue tumor immunohistochemistry update: Illustrative examples of diagnostic pearls to avoid pitfalls. Arch Pathol Lab Med 141(8): 1072-1091, 2017. PMID: 28745570. DOI: 10.5885/arpa.2016-0417-RA

45 Duff DJ, Guzman MA and Batanian JR: ABL1 gene involvement within a complex three-way translocation (2;9;4) in perineurioma characterized by molecular cytogenetic methods. Cancer Genet 207(6): 263-267, 2014. PMID: 25074247. DOI: 10.1016/j.cancergen.2014.05.012

46 Bekers EM, Groenen P, Verdijs MAJ, Raaijmakers-van Geloven WL, Roepman P, Vink R, Hiljuhs NDB, van Gorp JM, Bovee J, Creytens DH, Flanagan AM, Suurmeijer AHI, Mentzel T, Arbajian E and Flucke U: Soft tissue angiofibroma: Clinicopathologic, immunohistochemical and molecular analysis of 14 cases. Genes Chromosomes Cancer 56(10): 750-757, 2017. PMID: 28639284. DOI: 10.1002/gcc.22478

47 Jin Y, Moller E, Nord KH, Mandal N, von Steyven FV, Domanski HA, Marino-Enriquez A, Magnusson L, Nilsson J, Sciot R, Fletcher CD, Debic-Rychter M and Mertens F: Fusion of the AHRR and NCOA2 genes through a recurrent translocation t(5;8)(p15;q13) in soft tissue angiofibroma results in upregulation of aryl hydrocarbon receptor target genes. Genes Chromosomes Cancer 51(5): 510-520, 2012. PMID: 22337624. DOI: 10.1002/gcc.21939

48 Marino-Enriquez A and Fletcher CD: Angiofibroma of soft tissue: Clinicopathologic characterization of a distinctive benign fibrovascular neoplasm in a series of 37 cases. Am J Surg Pathol 36(4): 500-508, 2012. PMID: 22301504. DOI: 10.1097/PAS.0b013e31823de6ee

49 Edgar MA, Lauer SR, Bridge JA and Rizzo M: Soft tissue angiofibroma: Report of 2 cases of a recently described tumor. Hum Pathol 44(3): 438-441, 2013. PMID: 23261176. DOI: 10.1016/j.humpath.2012.08.021

50 Panagopoulos I, Gorounova L, Viset T and Heim S: Gene fusions AHR-NCFA2, NCOA2-ETV4, ETV4-AHRR, PHLA2-TCBK, and TBCK-PH-HA2 resulting from the translocations t(5;8;17) (p15;q13;q21) and t(4;5)(q24;q31) in soft tissue angiofibroma. Oncol Rep 36(5): 2455-2462, 2016. PMID: 27633981. DOI: 10.3892/or.2016.5096

51 Arbajian E, Magnusson L, Mertens F, Domanski HA, Valt von Steyven F and Nord KH: A novel GTF2I/NCOA fusion gene emphasizes the role of NCOA2 in soft tissue angiofibroma development. Genes Chromosomes Cancer 52(3): 330-331, 2013. PMID: 23225380. DOI: 10.1002/gcc.22033

52 Zamecnik M, Mukensnabl P and Chlumska A: Angiofibroma-like perineurioma. Report of a case. Cesk Patol 49(2): 86-88, 2013. PMID: 23641714.

53 Zhao M, Sun K, Li C, Zheng J, Yu J, Jin J and Xia W: Angiofibroma of soft tissue: Clinicopathologic study of 2 cases of a recently characterized benign soft tissue tumor. Int J Clin Exp Pathol 6(10): 2208-2215, 2013. PMID: 24133600.

54 Ma HJ, Huang HN, Li L, Chen S and Zhang YR: Clinicopathological characteristics of angiofibroma of soft tissue: Report of three cases. Int J Clin Exp Pathol 11(7): 3777-3784, 2018. PMID: 31949763.

55 Minidi-Romero AE, Maloney N, Bridge JA, Korkolopoulou P, Sakellariou S and Linos K: A concise review of angiofibroma of soft tissue: A rare newly described entity that can be encountered by dermatopathologists. J Cutan Pathol 47(2): 179-185, 2020. PMID: 31568567. DOI: 10.1111/cup.13580

56 Liu Y and Rohrschneider LR: The gift of gab. FEBS Lett 515(1-3): 1-7, 2002. PMID: 11943184. DOI: 10.1016/s0014-5793(02)02425-0

57 Nishida K and Hirano T: The role of gab family scaffolding adapter proteins in the signal transduction of cytokine and...
growth factor receptors. Cancer Sci 94(12): 1029-1033, 2003. PMID: 14662016. DOI: 10.1111/j.1349-7006.2003.tb01396.x

58 Scheffzek K and Welti S: Pleckstrin homology (ph) like domains - versatile modules in protein-protein interaction platforms. FEBS Lett 586(17): 2662-2673, 2012. PMID: 22728242. DOI: 10.1016/j.febslet.2012.06.006

59 Emory TS, Scheithauer BW, Hirose T, Wood M, Onofrio BM and Jenkins RB: Intraneural perineurioma. A clonal neoplasm associated with abnormalities of chromosome 22. Am J Clin Pathol 103(6): 696-704, 1995. PMID: 7785653. DOI: 10.1093/ajcp/103.6.696

60 Sciot R, Dal Cin P, Hagemeijer A, De Smet L, Van Damme B and Van den Berghe H: Cutaneous sclerosing perineurioma with cryptic NF2 gene deletion. Am J Surg Pathol 23(7): 849-853, 1999. PMID: 10403310. DOI: 10.1097/00000478-199907000-00015

61 Brock JE, Perez-Atayde AR, Kozakewich HP, Richkind KE, Fletcher JA and Vargas SO: Cytogenetic aberrations in perineurioma: Variation with subtype. Am J Surg Pathol 29(9): 1164-1169, 2005. PMID: 16096405. DOI: 10.1097/01.pas.0000158397.65190.9f

62 Mott RT, Goodman BK, Burchette JL and Cummings TJ: Loss of chromosome 13 in a case of soft tissue perineurioma. Clin Neuropathol 24(2): 69-76, 2005. PMID: 15803806.

63 Nishio J, Iwasaki H, Hayashi H, Nabeshima K and Naito M: Soft tissue perineurioma of the foot with 10q24 rearrangements: Unique MRI features with histopathologic correlation. Skeletal Radiol 43(7): 1017-1022, 2014. PMID: 24562506. DOI: 10.1007/s00256-014-1839-0

64 Lasota J, Fetsch JF, Wozniak A, Wasag B, Sciot R and Miettinen M: The neurofibromatosis type 2 gene is mutated in perineurial cell tumors: A molecular genetic study of eight cases. Am J Pathol 158(4): 1223-1229, 2001. PMID: 11290539. DOI: 10.1016/S0002-9440(10)64072-2

65 Klein CJ, Wu Y, Jentoft ME, Mer G, Spinner RJ, Dyck PJ, Dyck PJ and Mauermann ML: Genomic analysis reveals frequent TRAF7 mutations in intraneural perineuriomas. Am Neurol 81(2): 316-321, 2017. PMID: 28019650. DOI: 10.1002/ana.24854

66 Carter JM, Wu Y, Blessing MM, Folpe AL, Thorland EC, Spinner RJ, Jentoft ME, Wang C, Baheti S, Niu Z, Mauermann ML and Klein CJ: Recurrent genomic alterations in soft tissue perineuriomas. Am J Surg Pathol 42(12): 1708-1714, 2018. PMID: 30303818. DOI: 10.1097/PAS.0000000000001169

67 Mertens F, Dal Cin P, De Wever I, Fletcher CD, Mandahl N, Mitelman F, Rosai J, Rydholm A, Sciot R, Tallini G, van Den Berghe H, Vanni R and Willen H: Cytogenetic characterization of peripheral nerve sheath tumours: A report of the chmp study group. J Pathol 190(1): 31-38, 2000. PMID: 10640989. DOI: 10.1002/(SICI)1096-9896(200001)190:1<31::AID-PATH505>3.0.CO;2-%23

Received April 21, 2020
Revised May 22, 2020
Accepted June 1, 2020