

University of Groningen

**Variant WWTR1 gene fusions in epithelioid hemangioendothelioma-A genetic subset associated with cardiac involvement**

Suurmeijer, Albert J H; Dickson, Brendan C; Swanson, David; Sung, Yun-Shao; Zhang, Lei; Antonescu, Cristina R

*Published in:*  
 GENES CHROMOSOMES & CANCER

*DOI:*  
[10.1002/gcc.22839](https://doi.org/10.1002/gcc.22839)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
 Publisher's PDF, also known as Version of record

*Publication date:*  
 2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Suurmeijer, A. J. H., Dickson, B. C., Swanson, D., Sung, Y-S., Zhang, L., & Antonescu, C. R. (2020). Variant WWTR1 gene fusions in epithelioid hemangioendothelioma-A genetic subset associated with cardiac involvement. *GENES CHROMOSOMES & CANCER*, 59(7), 389-395. <https://doi.org/10.1002/gcc.22839>

**Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

**Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

**RESEARCH ARTICLE**

# Variant *WWTR1* gene fusions in epithelioid hemangioendothelioma—A genetic subset associated with cardiac involvement

Albert J. H. Suurmeijer<sup>1</sup> | Brendan C. Dickson<sup>2</sup> | David Swanson<sup>2</sup> | Yun S. Sung<sup>3</sup> | Lei Zhang<sup>3</sup> | Cristina R. Antonescu<sup>3</sup>

<sup>1</sup>Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>2</sup>Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada

<sup>3</sup>Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York

**Correspondence**

Cristina R. Antonescu, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10021, USA.

Email: antonesc@mskcc.org

**Funding information**

Center for Scientific Review, Grant/Award Numbers: CA008748, CA140146, CA217694; Kristin Ann Carr Foundation, Grant/Award Number: Kristin Ann Carr Foundation; Memorial Sloan-Kettering Cancer Center, Grant/Award Number: Cycle for Survival

**Abstract**

The genetic hallmark of epithelioid hemangioendothelioma (EHE) is a recurrent *WWTR1-CAMTA1* fusion, which is present in most cases bearing a conventional histology. A subset of cases is characterized by a distinct morphology and harbors instead of *YAP1-TFE3* fusion. Nevertheless, isolated cases lack these canonical fusions and remain difficult to classify. Triggered by an index case of a left atrial mass in a 76-year-old female with morphologic features typical of EHE, but which showed a *WWTR1-MAML2* fusion by targeted RNA sequencing, we searched our files for similar cases displaying alternative *WWTR1* fusions. A total of 6 EHE cases were identified with variant *WWTR1* fusions, four of them presenting within the heart. There were three females and three males, with a wide age range at diagnosis (21–76 years, mean 62, median 69). The four cardiac cases occurred in older adults (mean age of 72, equal gender distribution); three involved the left atrium and one the right ventricle. One case presented in the vertebral bone and one in pelvic soft tissue. Microscopically, all tumors had morphologic features within the spectrum of classic EHE; two of the cases appeared overtly malignant. All cases were tested by FISH and four were investigated by targeted RNA sequencing. Two tumors harbored *WWTR1-MAML2* fusions, one *WWTR1-ACTL6A*, and in three cases, no *WWTR1* partner was identified. Of the four patients with follow-up, two died of disease, one was alive with lung metastases, and the only patient free of disease was s/p resection of a T11 vertebral mass. Our findings report on additional genetic variants involving *WWTR1* rearrangements, with *WWTR1-MAML2* being a recurrent event, in a small subset of EHE, which appears to have predilection for the heart.

**KEYWORDS**

epithelioid hemangioendothelioma, heart, *WWTR1*, fusion

**1 | INTRODUCTION**

Epithelioid hemangioendothelioma (EHE) is a malignant vascular neoplasm, characterized by significant heterogeneity in both clinical presentation and prognosis.<sup>1</sup> Its clinical behavior is intermediate in

severity between the benign nature of hemangiomas and highly aggressive angiosarcomas.<sup>2</sup> Microscopically, conventional EHE is composed of nests and cords of epithelioid endothelial cells within a myxohyaline or sclerotic stroma; immunohistochemistry (IHC) usually demonstrates diffuse strong expression of ERG and CD31. The

majority of EHE (>90%) harbor unique *WWTR1-CAMTA1* fusions. This may be leveraged for diagnostic purposes by molecular methods, or surrogate IHC for *CAMTA1*.<sup>3-5</sup> A small subset of EHE bearing a distinct morphology, but overlapping clinical features, harbor instead of *YAP1-TFE3* fusion with concomitant nuclear *TFE3* overexpression.<sup>6</sup> A minority of tumors with otherwise typical histologic features, however, lack these canonical fusions thereby complicating molecular classification. Prompted by an index case of a cardiac EHE with a variant *WWTR1-MAML2* fusion identified by RNA sequencing, we studied five additional EHE cases from our molecular files with variant *WWTR1* fusion partners.

## 2 | MATERIALS AND METHODS

Clinical data, including age, gender, and anatomic site were retrieved from pathology reports. Hematoxylin and eosin-stained slides from biopsy and resection specimens were re-reviewed by two of us (A.S. and C.R.A.). Pathologic criteria for aggressive clinical behavior (aka malignant EHE) included moderate to severe nuclear atypia (nuclear enlargement and hyperchromasia), easily discerned nucleoli, and mitotic activity. In all cases, IHC for endothelial markers (CD31, ERG) was confirmed positive. Tumors were first tested by fluorescence in situ hybridization (FISH) for *WWTR1-CAMTA1* and *YAP1-TFE3* gene rearrangement, and if negative were subsequently tested by FISH for *WWTR1-MAML2* (the fusion gene found in the index case), or targeted RNA sequencing for possible other gene abnormalities. Follow-up information was obtained from the electronic medical records or referring pathologists. The study was approved by the Institutional Review Board.

### 2.1 | Fluorescence in situ hybridization

Custom probes were made from bacterial artificial chromosomes (BAC) clones flanking the genes of interest according to University of California Santa Cruz (UCSC) genome browser (<http://genome.ucsc.edu>) and obtained from BACPAC sources of Children's Hospital of Oakland Research Institute (Oakland, California; <https://bacpacresources.org/>). DNA from each BAC was isolated according to the manufacturer's instructions. The BAC clones were labeled with fluorochromes (fluorescent-labeled dUTPs, Enzo Life Sciences, New York, New York) by nick translation and validated on normal metaphase chromosomes. The 4  $\mu$ m-thick formalin-fixed paraffin-embedded (FFPE) slides were deparaffinized, pretreated, and hybridized with denatured probes. After overnight incubation, the slides were washed, stained with 4',6-diamidino-2-phenylindole, mounted with an antifade solution, and then examined on a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany) controlled by Isis 5 software (Metasystems, Newton, Massachusetts). Two hundred successive nuclei were examined using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany), controlled by Isis 5 software (Metasystems). A positive score was interpreted when at least 20% of the nuclei showed a

break-apart signal. Nuclei with incomplete set of signals were omitted from the score.

### 2.2 | Targeted RNA sequencing

Four cases were analyzed by targeted RNA sequencing, using RNA extracted from FFPE tissue with the Amsbio's ExpressArt FFPE Clear RNA Ready kit (Amsbio LLC, Cambridge, Massachusetts). The fragment length was assessed with an RNA 6000 chip on an Agilent Bioanalyzer (Agilent Technologies, Santa Clara, California). RNA-seq libraries were prepared using 20 to 100 ng total RNA with the TruSight RNA Fusion Panel (Illumina, San Diego, California). Targeted RNA sequencing was performed on an Illumina MiSeq platform. Reads were independently aligned with STAR (version 2.3) against the human reference genome (hg19) and analyzed by STAR-Fusion.

## 3 | RESULTS

We retrieved six EHE with variant *WWTR1* gene fusions. Their clinical and pathological features are summarized in Table 1. Of the four patients with available follow-up, two died of disease, at 9 and 15 months since diagnosis. One patient was alive with lung metastases, while one patient remained free of disease 70 months follow-up, s/p resection of a T11 vertebral mass.

### 3.1 | Alternative *WWTR1* fusions are associated with EHE presenting as cardiac tumors

Remarkably, 4/6 EHE with variant *WWTR1* gene rearrangements originated as cardiac tumors. All four patients with cardiac EHE were elderly (range 67-73 years), including three females and one male. Three tumors were localized in the left atrium, while one patient presented with a right ventricle mass and developed lung metastases. The three atrial EHE showed classic histologic features of relatively large epithelioid cells with eosinophilic and vacuolated cytoplasm arranged in radiating cords or solid sheets, embedded in a variable amount of myxohyaline mesenchymal stroma. The cells lacked significant nuclear atypia and mitoses were sparse (Figure 1). In contrast, the right ventricular EHE had overt malignant features, with increased cellularity and limited fibrous stroma. This EHE had a nested or cord-like architecture with relatively large epithelioid cells showing significant nuclear atypia and brisk mitotic activity (Figure 2). By IHC, all four cases stained positive for CD31 and ERG.

### 3.2 | EHE with variant *WWTR1* rearrangements may occasionally occur at other locations

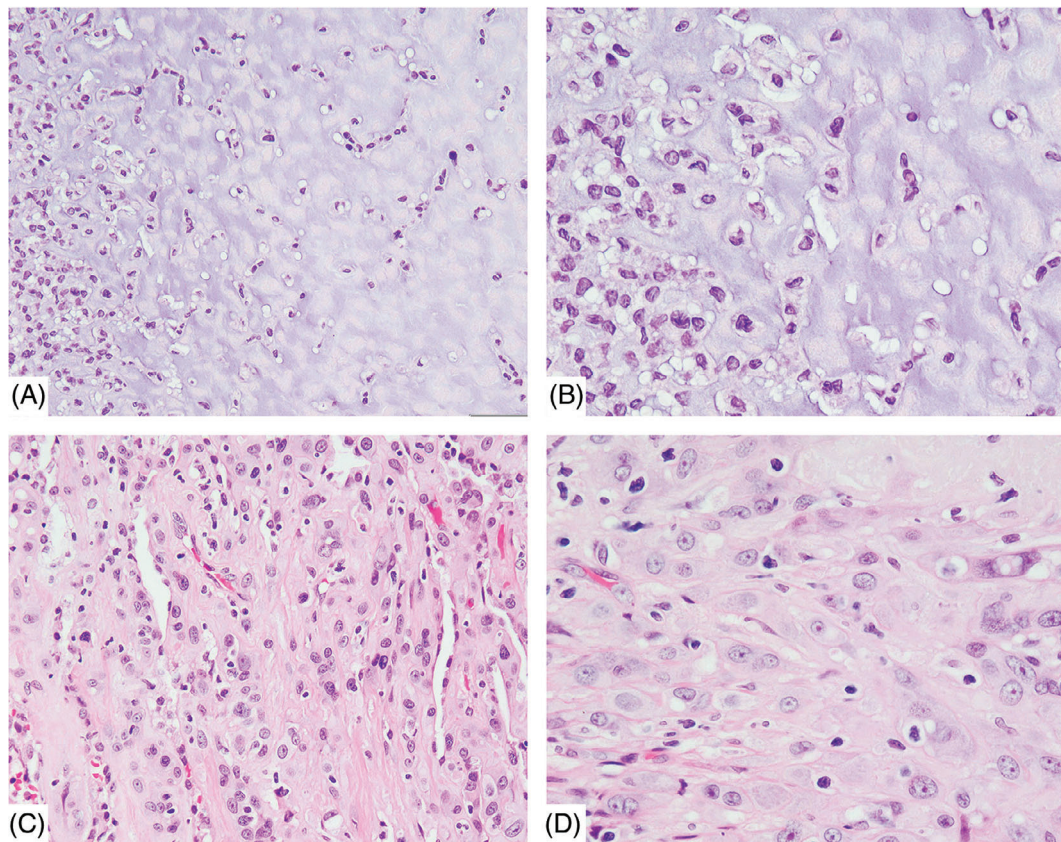
One case originated in bone and another in soft tissue. The first case, harboring a *WWTR1-MAML2* fusion, represented a bone tumor

**TABLE 1** Clinicopathological features of six EHE cases with variant *WWTR1* gene rearrangements

Case 1 <sup>a</sup>	<i>WWTR1-MAML2</i>	EHE	76/F	Heart, left atrium	N/A
Case 2	<i>WWTR1-MAML2</i>	EHE	21/M	Bone, vertebra T11	NED, 70 months (s/p resection)
Case 3 <sup>a</sup>	<i>WWTR1-ACTL6A</i>	Malignant EHE	73/F	Heart, right ventricle	DOD, 9 months
Case 4 <sup>a</sup>	<i>WWTR1</i> rearrangement	EHE	72/F	Heart, left atrium	DOD, 15 months (s/p chemo Adriamycin +DTIC), soft tissue metastases
Case 5 <sup>a</sup>	<i>WWTR1</i> rearrangement	EHE	67/M	Heart, left atrium	Lung metastases at diagnosis
Case 6	<i>WWTR1</i> rearrangement	Malignant EHE	65/M	Pelvic mass	Recent case

Abbreviation: EHE, epithelioid hemangioendothelioma.

<sup>a</sup>Cases tested by targeted RNA sequencing (in case 4 RNAseq failed, case 5 was negative); N/A, not available.



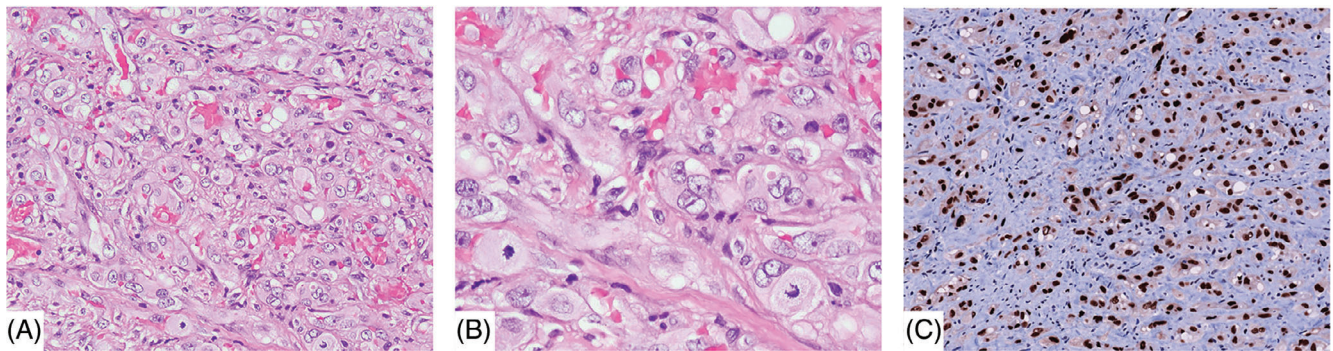
**FIGURE 1** Morphologic spectrum of cardiac atrial tumors with *WWTR1* variant fusions. Bland epithelioid cells arranged in single files and cords within an abundant myxochondroid matrix (A, B, case 1). A more cellular lesion showing compact epithelioid cells with dense eosinophilic cytoplasm arranged in solid sheets with a less conspicuous fibrotic stromal component (C, D, case 5) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

involving the 11th thoracic vertebra of a 21-year-old male. A bone needle biopsy revealed a cellular but otherwise classic EHE composed of randomly arranged epithelioid cells without nuclear atypia or increased mitotic activity. The tumor cells stained positive for endothelial markers. The second case concerned a large pelvic mass in a 65-year-old male. This EHE consisted of small trabeculae with malignant epithelioid tumor cells, showing nuclear and nucleolar pleomorphism and easily discerned mitoses. The tumor cells were surrounded by scant fibrous stroma, which contained many neutrophilic and eosinophilic granulocytes (Figure 3). In this case, a diagnosis of

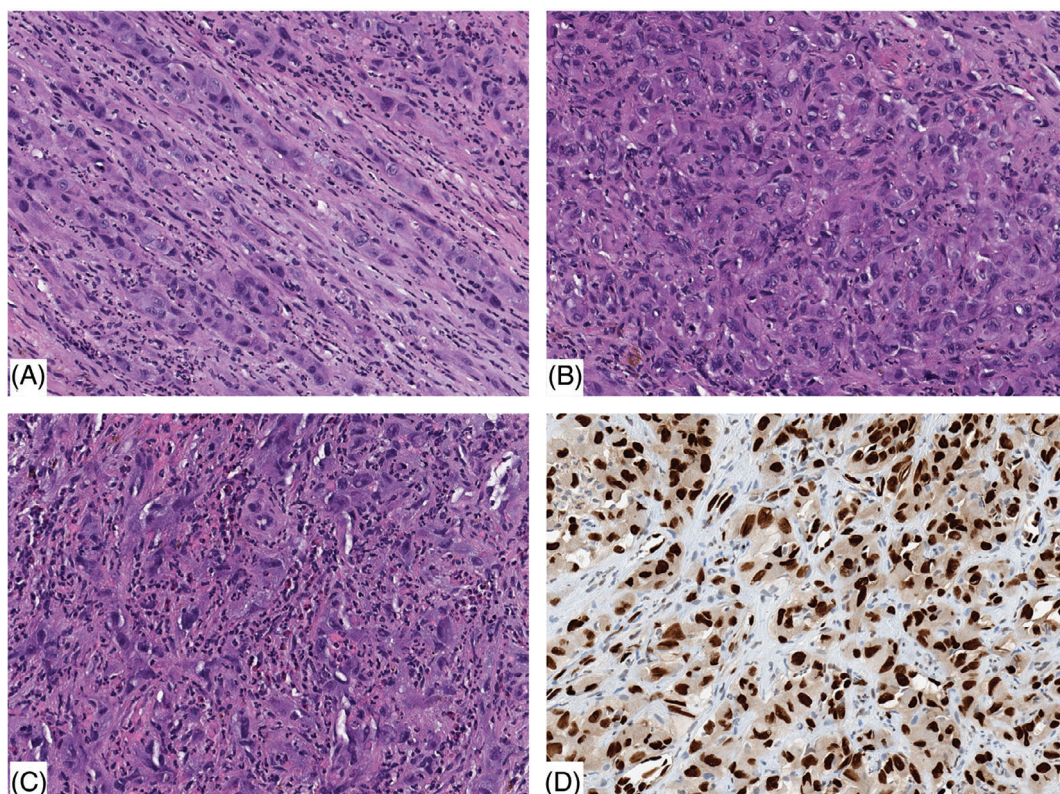
malignant EHE was established by IHC with expression of ERG and CD31. Moreover, FISH revealed rearrangement of *WWTR1*, but the tumor lacked rearrangement of both *MAML2* and *CAMTA1* genes. NGS in this case failed to identify any fusion gene candidate.

### 3.3 | Molecular findings

In the index case (case 1), targeted RNA sequencing revealed a *WWTR1-MAML2* fusion gene, composed of the first 5 exons of



**FIGURE 2** A malignant EHE presenting as a right ventricular mass with lung metastases. The tumor was composed of sheets of enlarged epithelioid cells with abundant pale eosinophilic cytoplasm and enlarged nuclei with moderate atypia and prominent nucleoli. Mitotic figures were abundant. Tumor cells showed strong immunoreactivity for ERG (A-C, case 3) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

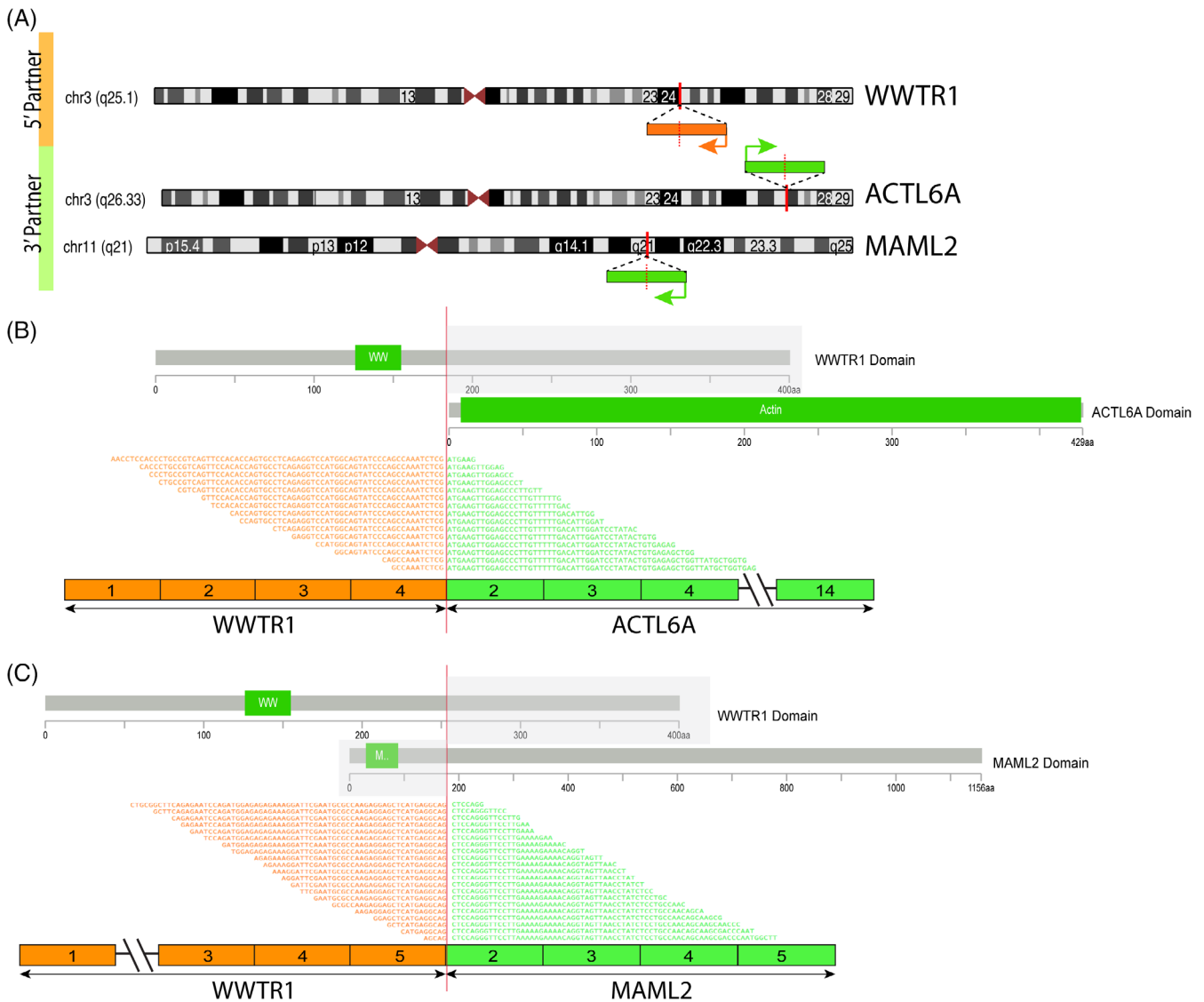


**FIGURE 3** A malignant EHE with *WWTR1* rearrangement only, presenting as a large pelvic mass in a 65-year-old male. The tumor is composed of large epithelioid to plump ovoid cells with abundant eosinophilic cytoplasm, arranged in cords, A; solid sheets, B; with variable nuclear pleomorphism, C; prominent nucleoli and intermixed inflammatory cells including eosinophils. D, The tumor cells show strong nuclear reactivity for ERG [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

*WWTR1* fused to *MAML2* exons 2-5 (Figure 4). In case 3, a malignant EHE in the right ventricle, targeted RNA sequencing revealed a novel *WWTR1-ACTL6A* gene fusion, composed of the first 4 exons of *WWTR1* fused to most of the *ACTL6A* gene (exons 2-14) (Figure 4). Moreover, three tumors showed *WWTR1* rearrangements by FISH (without *MAML2* and *CAMTA1* abnormalities).

## 4 | DISCUSSION

In the past decade, several molecular genetic discoveries have contributed significantly to the pathologic subclassification of epithelioid vascular neoplasms.<sup>7</sup> In this respect, two molecular subsets of EHE have been defined, characterized by recurrent gene fusions *WWTR1-CAMTA1* (90%) and *YAP1-TFE3* (10%), sharing overlapping



**FIGURE 4** Diagrammatic representation of two *WWTR1* fusion variants identified on targeted RNA sequencing. A, Chromosomal location of *WWTR1* gene locus in 3q25.1, *ACTL6A* in 3q26.33 and *MAML2* in 11q21; red vertical lines depict the genomic breakpoint locus. Arrows show the direction of transcription of each gene. B, *WWTR1-ACTL6A* transcript is composed of the first four exons of *WWTR1* fused to most of *ACTL6A* (exons 2-14). C, *WWTR1-MAML2* transcript composed of the first five exons of *WWTR1* gene fused to most of *MAML2* gene (exons 2-5). The protein domains of each of the genes involved is also schematically depicted [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

clinical presentations but associated with distinct morphologic appearances.<sup>3,4,6</sup> EHE is a low-grade malignant vascular tumor with clinical and morphologic features intermediate between benign epithelioid hemangioma and high-grade epithelioid angiosarcoma.<sup>3,4,6,8</sup> Triggered by a handful of cases lacking these canonical genetic abnormalities, we investigated a small cohort of EHE harboring alternative *WWTR1* fusions. By RNA sequencing, we identified two novel gene fusions, showing that *WWTR1* may partner with either *MAML2* or *ACTL6A* in EHE. To date, these fusion genes have not been reported in other neoplasms.

*WWTR1* and its paralogue *YAP1* encode the proteins TAZ and YAP, respectively, which are downstream effectors of the Hippo tumor suppressor pathway and function as regulators of TEAD-dependent transcription. In *WWTR1-CAMTA1* fusion-positive EHE,

*CAMTA1* binding transports the chimeric TAZ-*CAMTA1* protein from the cytoplasm to the nucleus, resulting in uncoupling of the Hippo pathway and activation of a TAZ-like transcriptional program, contributing to oncogenic transformation.<sup>9</sup>

Interestingly, recurrent *YAP1-MAML2* fusion genes were recently described in a large group of skin adnexal tumors (poromas)<sup>10</sup> and in uncommon biphasic thymic tumors (metaplastic thymomas)<sup>10</sup>; consistently retaining the N-terminal TEAD-binding domains of *YAP1* within the chimeric oncoprotein. Furthermore, *YAP1* fusion products accumulate in the nuclei of immortalized human epidermal keratinocytes, where they activate TEAD-dependent transcription, and promoted cell growth of mouse embryonic fibroblasts.<sup>10</sup> *ACTL6A* is a subunit of the SWI/SNF (BAF) complex and a regulator of various oncogenes, including the Hippo pathway regulator *WWC1*. Moreover, as observed

in human glioma cells, *ACTL6A* enhances the transcriptional activity of nuclear YAP/TAZ by inhibition of YAP proteasomal protein degradation.<sup>11</sup>

In soft tissue locations, EHE has a broad anatomic distribution with a predilection for the extremities. Approximately half of cases are angiocentric and appear to arise from a large caliber blood vessel. EHE affects all age groups but is most common in the second decade of life. There is an almost equal gender distribution. Soft tissue EHE larger than 3 cm and with increased mitotic rate (>3 mitoses in 50 HPF) are considered high-risk tumors apt to develop metastases in up to 40% of cases, whereas smaller EHE with low nuclear grade and scant mitoses are considered to be low-risk tumors.<sup>12</sup> In a large cohort of 93 molecularly confirmed EHE involving different sites, it was found that most soft tissue EHE are solitary.<sup>1</sup> In addition to tumor grade, the presence of multifocal disease, pleural involvement, and lymph node or distant metastases had significant power in predicting prognosis. Moreover, EHE with *WWTR1-CAMTA1* fusions had a less favorable clinical outcome than EHE with *YAP1-TFE3*, with a five-year survival rate of 59% and 86%, respectively.<sup>1</sup>

In this modest series of EHE with alternative *WWTR1* abnormalities, the majority (4/6) of cases represented cardiac tumors presenting in elderly patients. This is a remarkable observation, since most EHE originate in soft tissue and bone locations, and other visceral organs (in particular lung/pleura and liver), and present in adult patients with a wide age range. Of the four cardiac EHE, three occurred in the atria and showed classic histology with cords and nests of endothelial cells surrounded by variable myxohyaline stroma. This architectural pattern was highlighted by immunostaining for the endothelial markers ERG and CD31. In the three atrial EHE, the tumor cells had round nuclei and moderate amounts of eosinophilic cytoplasm, occasionally with intracytoplasmic vacuoles. The fourth cardiac EHE originated in the right ventricle and this tumor had malignant histologic features with aggressive clinical behavior, with development of lung deposits.

Primary cardiac tumors are uncommon. Among benign cardiac tumors, cardiac myxoma is most prevalent and frequently (in about 85% of cases) attached to the left atrial septum. The large majority of cardiac myxomas are sporadic tumors, but around 5% are a manifestation of the Carney complex.<sup>13</sup> Both manifestations are associated with *PRKAR1A* gene mutations.<sup>14</sup> Histologically, cardiac myxoma may be mistaken for EHE, since both neoplasms consist of cords of epithelioid tumor cells suspended in myxohyaline matrix. However, in cardiac myxoma the tumor cells usually form a perivascular reticular network, a histological growth pattern that becomes clearly visible with IHC staining for calretinin.<sup>15</sup>

Intimal sarcoma and angiosarcoma are the most frequent malignant cardiac tumors. Whereas intimal sarcoma may present in all heart chambers, cardiac angiosarcoma nearly always arises in the right heart. Morphologically, intimal sarcoma displays a variegated phenotype, but at the low-grade end of the spectrum, tumors contain myxoid areas of low cellularity. However, most intimal sarcomas are characterized by primarily spindle-shaped cells with variable nuclear pleomorphism and hyperchromasia. Moreover, at the molecular level, *MDM2* and *CDK4* gene amplification or overexpression may help in this distinction.<sup>16</sup> Cardiac angiosarcoma represents a clinically

aggressive high-grade sarcoma usually composed of slit-like channels or cellular fascicles of eosinophilic spindle cells, often associated with necrosis, increased mitotic activity and hemorrhagic stroma. In contrast to EHE, angiosarcomas have a complex molecular signature<sup>17</sup> and lack recurrent *WWTR1* gene rearrangements.<sup>7</sup>

The differential diagnosis of EHE mainly includes other epithelioid vascular tumors with IHC expression of ERG and CD31, in particular epithelioid hemangioma (EH) and pseudomyogenic hemangioendothelioma (PHE). Classic EH of soft tissue and bone has a wide age range, no gender predilection, and variable anatomic distribution. Occurrence in visceral sites is extremely uncommon. Morphologically, EH of soft tissue and bone has a lobular growth pattern, with overt vascular channel formation lined by epithelioid endothelial cells and surrounded by SMA-positive pericytes. However, the morphology of a subset of EH with cellular and atypical features may closely resemble EHE. In these challenging cases, molecular genetic studies may be of great help, as virtually all EHE harbor either *WWTR1-CAMTA1* (90%) or *YAP1-TFE3* (10%) fusion products, whereas about half of cellular/atypical EH harbor *FOS* or *FOSB* fusions with different partners.<sup>18</sup> PHE is another distinctive but rare epithelioid endothelial neoplasm of soft tissue and bone.<sup>19</sup> Most often, PHE presents as multicentric nodules in superficial and deep soft tissue of the extremities in young adult patients. PHE has a high recurrence rate and distant metastases may occur, albeit infrequently (around 5%). PHE is composed of fascicles of large spindle or epithelioid tumor cells with eosinophilic cytoplasm resembling myoid cells. By molecular genetics, more than half of PHE harbor *FOSB* fusions with *ACTB*, *SERPINE1* or *WWTR1*.<sup>20-22</sup>

In conclusion, with the advent of targeted RNA sequencing the molecular subclassification of vascular tumors, including EHE, continues to evolve. Our results demonstrate that a subset of cases contain novel *WWTR1* fusion partners, including *MAML2* and *ACTL6A*, along with potentially other gene partners, which showed a striking preference for cardiac presentation. This anatomic location is very rarely encountered among EHE cases with the more typical fusions. Clearly, larger series of EHE with variant *WWTR1* fusions are needed for more definitive clinicopathological correlations, including prognostication.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

Cristina R. Antonescu  <https://orcid.org/0000-0002-9717-8205>

## REFERENCES

- Rosenbaum E, Jadeja B, Xu B, et al. Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets. *Mod Pathol*. 2019. <https://doi.org/10.1038/s41379-019-0368-8>.
- Fletcher CDM, Bridge JA, Hogendoorn PC, Mertens F. *WHO Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon, France: IARC; 2013.
- Errani C, Zhang L, Sung YS, et al. A novel *WWTR1-CAMTA1* gene fusion is a consistent abnormality in epithelioid hemangioendothelioma

- of different anatomic sites. *Genes Chromosomes Cancer*. 2011;50:644-653. <https://doi.org/10.1002/gcc.20886>.
4. Tanas MR, Sboner A, Oliveira AM, et al. Identification of a disease-defining gene fusion in epithelioid hemangioendothelioma. *Sci Transl Med*. 2011;3(98):98ra82.
  5. Doyle LA, Fletcher CDM, Hornick JL. Nuclear expression of CAMTA1 distinguishes epithelioid hemangioendothelioma from histologic mimics. *Am J Surg Pathol*. 2016;40:94-102.
  6. Antonescu CR, Le Loarer F, Mosquera JM, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. *Genes Chromosomes Cancer*. 2013;52(8):775-784. <https://doi.org/10.1002/gcc.22073>.
  7. Antonescu C. Malignant vascular tumors—an update. *Mod Pathol*. 2014;27(suppl 1):S30-S38.
  8. Flucke U, Vogels RJC, de Saint Aubain Somerhausen N, et al. Epithelioid hemangioendothelioma: clinicopathologic, immunohistochemical, and molecular genetic analysis of 39 cases. *Diagn Pathol*. 2014;9:131.
  9. Tanas MR, Ma S, Jadaan FO, et al. Mechanism of action of a WWTR1 (TAZ)-CAMTA1 fusion oncoprotein. *Oncogene*. 2016;35:929-938. <https://doi.org/10.1038/onc.2015.148>.
  10. Sekine S, Kiyono T, Ryo E, et al. Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma. *J Clin Invest*. 2019;130:3827-3832.
  11. Ji J, Xu R, Zhang X, et al. Actin like-6A promotes glioma progression through stabilization of transcriptional regulators YAP/TAZ. *Cell Death Dis*. 2018;9:517.
  12. Deyrup AT, Tighiouart M, Montag AG, Weiss SW. Epithelioid hemangioendothelioma of soft tissue: a proposal for risk stratification based on 49 cases. *Am J Surg Pathol*. 2008;32:924-927.
  13. Burke A, Tavora F. The 2015 WHO classification of tumors of the heart and pericardium. *J Thorac Oncol*. 2016;11:441-452.
  14. Maleszewski JJ, Larsen BT, Kip NS, et al. PRKAR1A in the development of cardiac myxoma: a study of 110 cases including isolated and syndromic tumors. *Am J Surg Pathol*. 2014;38:1079-1087.
  15. Terracciano LM, Mhawech P, Suess K, et al. Calretinin as a marker for cardiac myxoma. Diagnostic and histogenetic considerations. *Am J Clin Pathol*. 2000;114:754-759. <https://doi.org/10.1309/NR6G-T872-F090-LBRW>.
  16. Neuville A, Collin F, Bruneval P, et al. Intimal sarcoma is the most frequent primary cardiac sarcoma: clinicopathologic and molecular retrospective analysis of 100 primary cardiac sarcomas. *Am J Surg Pathol*. 2014;38:461-469.
  17. Leduc C, Jenkins SM, Sukov WR, Rustin JG, Maleszewski JJ. Cardiac angiosarcoma: histopathologic, immunohistochemical, and cytogenetic analysis of 10 cases. *Hum Pathol*. 2017;60:199-207. <https://doi.org/10.1016/j.humpath.2016.10.014>.
  18. Huang SC, Zhang L, Sung YS, et al. Frequent FOS gene rearrangements in epithelioid hemangioma: a molecular study of 58 cases with morphologic reappraisal. *Am J Surg Pathol*. 2015;39:1313-1321.
  19. Hornick JL, Fletcher CDM. Pseudomyogenic hemangioendothelioma: a distinctive, often multicentric tumor with indolent behavior. *Am J Surg Pathol*. 2011;35:190-201.
  20. Walther C, Tayebwa J, Lilljebjörn H, et al. A novel SERPINE1-FOSB fusion gene results in transcriptional up-regulation of FOSB in pseudomyogenic haemangioendothelioma. *J Pathol*. 2014;232(5):534-540. <https://doi.org/10.1002/path.4322>.
  21. Agaram NP, Zhang L, Cotzia P, Antonescu CR. Expanding the spectrum of genetic alterations in pseudomyogenic hemangioendothelioma with recurrent novel ACTB-FOSB gene fusions. *Am J Surg Pathol*. 2018;42:1653-1661.
  22. Panagopoulos I, Lobmaier I, Gorunova L, Heim S. Fusion of the genes WWTR1 and FOSB in pseudomyogenic hemangioendothelioma. *Cancer Genomics Proteomics*. 2019;16(4):293-298. <https://doi.org/10.21873/cgp.20134>.

**How to cite this article:** Suurmeijer AJH, Dickson BC, Swanson D, Sung YS, Zhang L, Antonescu CR. Variant WWTR1 gene fusions in epithelioid hemangioendothelioma—A genetic subset associated with cardiac involvement. *Genes Chromosomes Cancer*. 2020;1-7. <https://doi.org/10.1002/gcc.22839>