CARMN fusions and *PDGFRB* mutations highlight key differences among cutaneous tumors with myopericytic differentiation

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TO THE EDITOR

Cutaneous tumors with myopericytic differentiation (PTs) are a family of soft tissue tumors arising from pericytes, encompassing myopericytoma (MPC), glomus tumor (GT), and angioleiomyoma (ALM). These tumors represent a morphological continuum, with some cases showing overlapping features (Figure 1a–c). Molecular studies of PTs to date have focused on either their mutational profile or gene fusions (Agaram et al, 2020; Hung and Fletcher, 2017; Iwamura et al, 2023; Mosquera et al, 2013; Panagopoulos et al, 2023); however, it remains to be determined how these alterations overlap and whether they can explain the subtle morphological differences between these subtypes. Thus, we collated an international cohort of 168 formalin-fixed, paraffin-embedded PTs, comprised of MPC (n = 42), GT (n = 45), and ALM (n = 81) cases, none of which included the malignant counterparts. We performed tumor and normal DNA whole-exome sequencing and tumor RNA exome-capture transcriptome sequencing from cases for which both tumor and matched normal tissue were available ('matched' cohort) or for which tumor-only tissue was available ('unmatched' cohort).

Across the matched and unmatched MPC cohorts, we identified mutations in *KRAS* (p.Q61H and p.G12R, 1/42 cases each), which have not been reported in this tumor type. In agreement with previous MPC studies (Hung and Fletcher, 2017; Iwamura et al, 2023), we observed mutations in *PDGFRB* and *NOTCH3* (5 of 42 and 3 of 42 cases, respectively). *PDGFRB* mutations were found at several hotspots, including p.E570_G576delinsDT, p.V568G, p.I538N, p.L539P, and those previously reported in MPC (p.K653E and p.N666K) (Hung and Fletcher, 2017; Iwamura et al, 2023). Considering fusions, 2 were identified in the MPC cases: *CARMN::TXK* (28 of 42, 67% cases) and *CARMN::NOTCH2* (with its reciprocal in 1 of 42 cases). Most *CARMN::TXK* fusions with the highest read support per sample shared genomic breakpoint coordinates at *CARMN*, a highly expressed smooth muscle–specific long noncoding RNA, and tyrosine kinase *TXK*, on exons 2 or 3. These findings are consistent with the only previous report of *CARMN::TXK* in a case of ALM (Panagopoulos et al, 2023), where the effect of *TXK* overexpression by promoter replacement is proposed (Panagopoulos et al, 2023).

In the matched GT cohort, there were 4 recurrently mutated genes, specifically *NF1*, *PCLO*, *PDGFRB*, and *TEK* (2 of 24 cases each). Previous molecular studies of GT have reported mutations in *PDGFRB* and *NOTCH3* (Hung and Fletcher, 2017; Iwamura et al, 2023), and when considering both matched and unmatched GT cohorts, *PDGFRB* and *NOTCH3* were mutated in 10 of 45 (22%) and 1 of 45 (2%) cases, respectively. The *PDGFRB* mutations occurred at the same hotspots previously reported in MPC, including p.Y562C (Hung and Fletcher, 2017; Iwamura et al, 2023). Regarding fusions, 3 were identified in GT (with their reciprocal fusions also noted), specifically *CARMN::NOTCH2* (19 of 45 cases), as previously reported (Agaram et al, 2020; Mosquera et al, 2013), and the in-frame fusions *ACTB::NOTCH3* (2 of 45 cases) and *CACNA2D3::MYH9* (1 of 45 cases). In *CARMN::NOTCH2* cases, the fusion incorporated the first exons of *CARMN* and the C-terminal end of *NOTCH2*, with 3 different recurrent breakpoints identified on exon 27 (as previously reported [Mosquera et al, 2013]), 28, or 29.

In the matched ALM cohort, the only recurrently mutated gene was *PIK3CA* (2 of 34 cases), which has not been reported in this tumor type. Previous molecular studies of ALM have reported mutations in *PDGFRB* and *NOTCH3* (Hung and Fletcher, 2017; Iwamura et al, 2023). Considering both ALM cohorts, *PDGFRB* was mutated in 2 of 81 (2%) cases, and *NOTCH1* and *NOTCH2* were mutated in 1 tumor sample each. No recurrent fusion events were identified, although we observed an in-frame *THBS1::IGF1R* fusion (1 of 81 cases)—recently identified as a fusion gene in a myopericytic tumor (Kato et al, 2024). Identified fusions with *CARMN* were *CARMN::TXK*, as previously reported (Panagopoulos et al, 2023), and, to our knowledge, the previously unreported fusion *CARMN::PIK3CA* (1 of 81 cases each).

Taking the transcriptome data from each PT in this study and performing principal component analysis, k-nearest neighbors, and shared nearest neighbor clustering analysis, we identified 5 transcriptional clusters (Figure 2a). When the histopathological diagnosis was assigned to each tumor, clusters 1 and 5 only contained ALM cases; cluster 2 was predominantly MPC, with a few ALM and GT cases; and clusters 3 and 4 were predominantly GT, with a few ALM and MPC cases (Figure 2b). Cases that showed morphological features of more than 1 subtype explained some of the overlap of tumor types between the clusters (Figure 2b). Fusions with *CARMN* as one of the partners

Abbreviations: ALM, angioleiomyoma; GT, glomus tumor; MPC, myopericytoma; PT, cutaneous tumors with myopericytic differentiation

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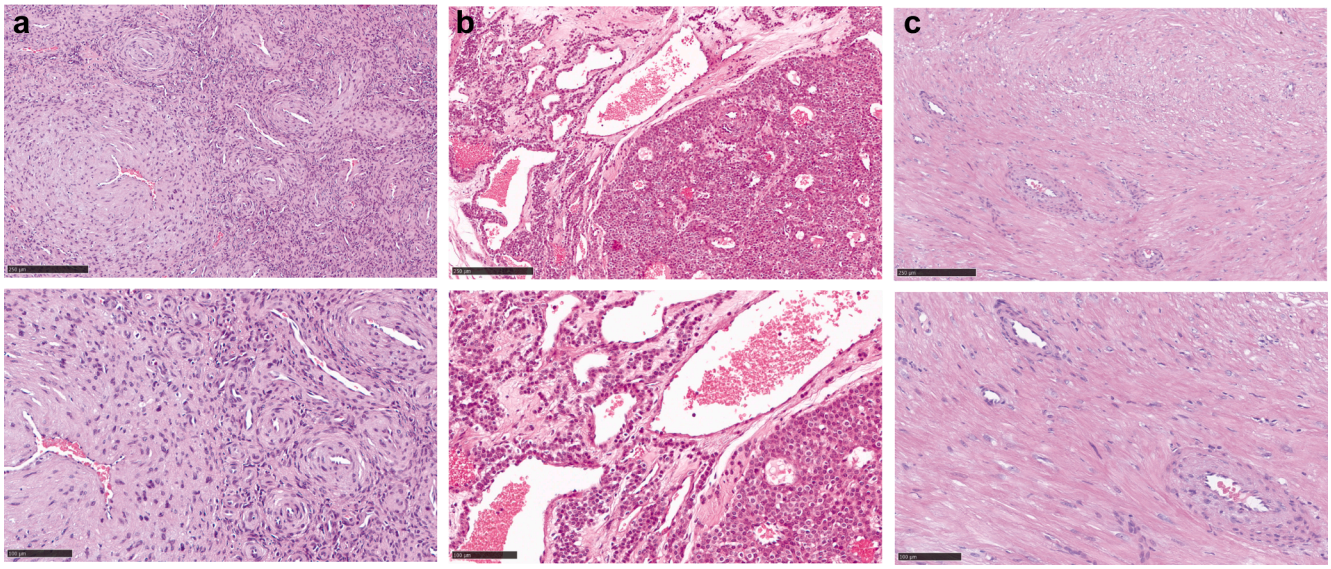

Figure 1. Histopathology of cutaneous tumors with myopericytic differentiation. Representative images of H&E-stained sections of (**a**) myopericytoma, (**b**) glomus tumor, and (**c**) angioleiomyoma. The upper panel is ×1.25 magnification with bar representing 2.5 mm and the lower panel is ×20 magnification with bar representing 100 μm.

demonstrated that *CARMN::TXK* was primarily found in MPC (n = 1 ALM case) (Figure 2c). Furthermore, the presence of *CARMN* fusions and *PDGFRB* mutations was mutually exclusive (adjusted P = .0488 and .0052 in MPC and GT, respectively; Fisher's exact test, Benjamini–Hochberg correction) (Figure 2d). *CARMN::NOTCH2* were only found in cluster 3 of the GT cases, whereas cluster 4 of the GT cases contained most of the tumors with *PDGFRB* mutations. Considering the downstream signaling pathways of the CARMN fusion partners and PDGFRB, it is interesting to note that although PDGFRB signals through the phosphoinositide 3-kinase pathway, of which PIK3CA is a component, there is no overlap in the PDGFRB and NOTCH2 or TXK signaling pathways.

Thus, the presence of a *CARMN* fusion or *PDGFRB* mutation in a large proportion of MPC and GT but rarely ALM highlights that although these 3 types of PTs represent a morphological continuum, MPC and GT possess key molecular similarities and are generally genetically distinct from ALM.

ETHICS STATEMENT

Ethical approval for the use of all patient samples in this project was obtained by a local committee at the institution of origin and from Research Governance at the Wellcome Sanger Institute. This study is part of the DERMATLAS Project, which has been approved by the NHS Health Research Authority (Research Ethics Committee reference 21/PR/1024, IRAS project identification 304621). The study is anonymized and linked, and signed patient consent was given for the use of their tissue samples and associated clinical metadata for research purposes at the time the samples were collected for diagnostic purposes.

DATA AVAILABILITY STATEMENT

The sequencing data are available in the European Genome and Phenome Archive repository as follows: angioleiomyoma (whole-exome sequencing, https://ega-archive.org/studies/EGAS00001005710; RNA exome-capture transcriptome sequencing, https://ega-archive.org/studies/EGAS00001005711), glomus tumor (whole-exome sequencing, https://ega-archive.org/studies/EGAS00001005712; RNA exome-capture transcriptome sequencing, https://ega-archive.org/studies/EGAS00001005713), and myopericytoma (whole-exome sequencing, https://ega-archive.org/studies/EGAS00001006676; RNA exome-capture transcriptome sequencing, https://ega-archive.org/studies/EGAS00001006684). For any data queries, contact the corresponding author.

KEYWORDS

Angioleiomyoma; CARMN; Glomus tumor; Myopericytoma; Pericytic tumor

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: DJA, TB, MJA, IF; Formal Analysis: MDCV-H, SC, KW, JB, IV; Funding Acquisition: DJA; Investigation: EA, EF, MJA, IF, TB, LvdW; Project Administration: LvdW; Resources: PWH, NdSA, ELC, WM, AKA, NR, PF, MAW, CM, SDB, MJA, IF, TB; Software: MDCV-H, SC, KW, JB, IV; Visualization: MDCV-H; Writing - Original Draft Preparation: LvdW.; Writing - Review and Editing: MDCV-H, KW, PWH, MJA, IF, TB, LvdW, DJA

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMs)

The author(s) did not use AI/LLM in any part of the research process and/or manuscript preparation.

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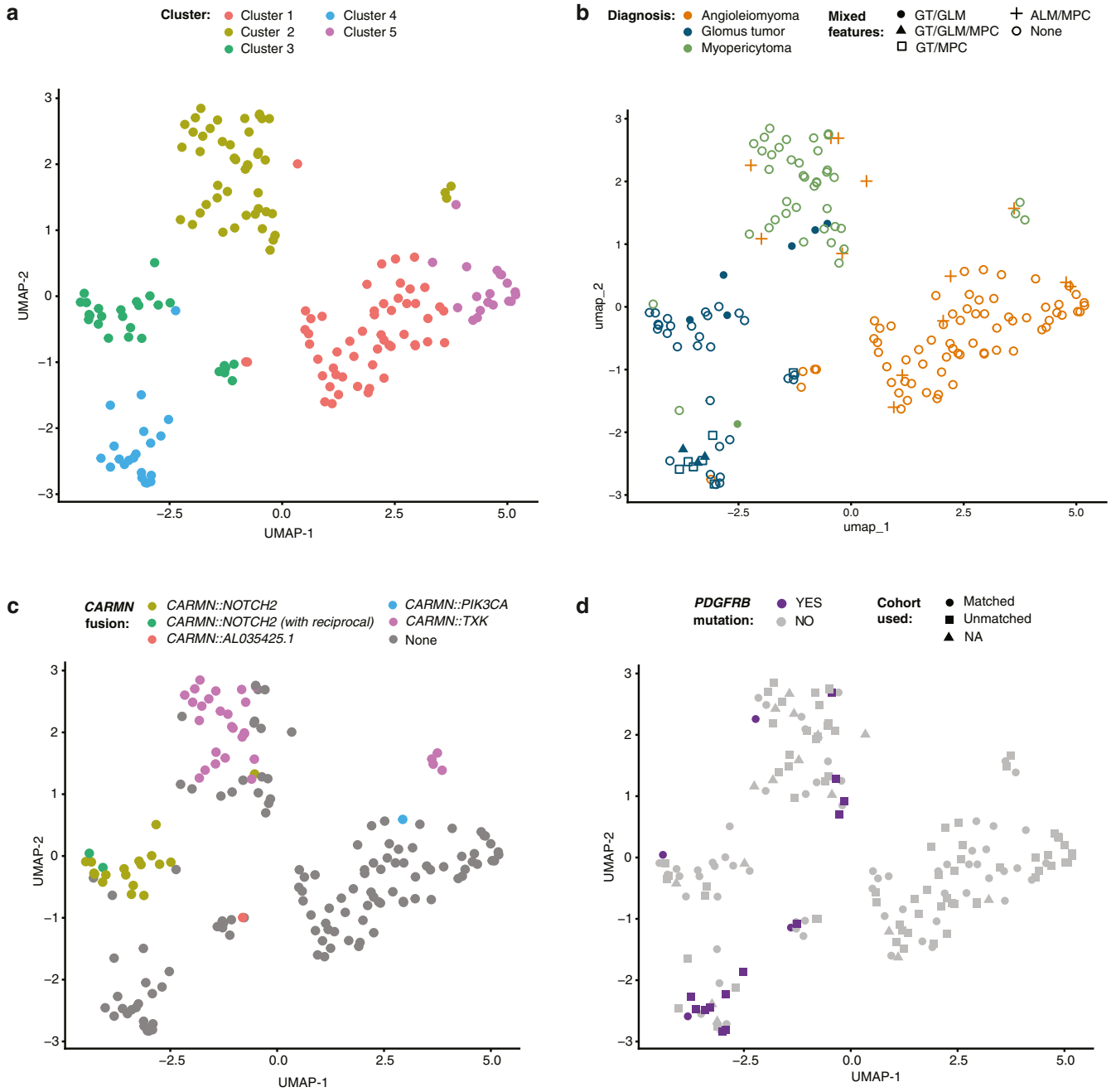

Figure 2. Transcriptomic clustering and molecular features of cutaneous tumors with myopericytic differentiation. **(a)** UMAP showing the annotation of the 5 clusters derived from the shared nearest neighbor unsupervised clustering analysis from the tumor transcriptomes. **(b)** Distribution of the pathological diagnosis within the 5 clusters; diagnosis is indicated by color, with the presence of mixed features indicated by the different shapes. **(c)** Distribution of all the *CARMN* gene fusion events within the 5 clusters; the fusion partners and fusion-negative samples indicated by color. Also showing the noncoding fusion, *CARMN::AL035425.1*. **(d)** Distribution of the tumors with protein-altering *PDGFRB* mutations within the 5 clusters; the mutational status indicated by color, and the cohort used for somatic calling is indicated by shape. NA, not applicable; UMAP, Uniform Manifold Approximation and Projection.

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