



# Metaplastic thymoma: a distinctive thymic neoplasm characterized by *YAP1-MAML2* gene fusions

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## Abstract

Metaplastic thymomas are rare biphasic thymic tumors that are characteristically well-circumscribed, confined to the thymus, and follow a benign to indolent clinical course. Their relationship to other thymic neoplasms remains unclear, and their molecular characteristics have not been defined. We report for the first time recurrent translocation events in metaplastic thymomas involving the Yes Associated Protein 1 (*YAP1*) and Mastermind Like Transcriptional Coactivator 2 (*MAML2*) genes. Eight metaplastic thymomas were retrieved from two institutions' archives over a 21-year period. Paraffin-embedded material from all cases underwent targeted DNA-based hybrid capture next-generation sequencing. Cases showing no somatic alterations subsequently underwent targeted RNA sequencing. Allele-specific real-time polymerase chain reaction was performed to detect *GTF2I* c.74146970T>A (p.L424H) mutations. All cases showed characteristic histologic features of metaplastic thymoma and demonstrated no local recurrence or distant metastatic disease at 1–22 years of follow-up. Six of eight cases were successfully sequenced, all showing *YAP1-MAML2* fusions; in four cases the fusions were detected by DNA sequencing and in two cases by RNA sequencing. Two distinct products were identified: 5' *YAP1* exon 1 fused to 3' *MAML2* exons 2–5 or 5' *YAP1* exons 1–5 fused to 3' *MAML2* exons 2–5. All cases underwent allele-specific real-time polymerase chain reaction and demonstrated no *GTF2I* L424H mutations. Metaplastic thymoma is a distinct, clinically indolent thymic epithelial neoplasm characterized by *YAP1-MAML2* fusion and lacking the *GTF2I* mutations found in Type A and AB thymomas.

## Introduction

Metaplastic thymoma is a rare biphasic tumor of the thymus typically found incidentally as a rounded anterior mediastinal mass in asymptomatic patients [1, 2], or in association with thymic cysts [3]. When originally described, this tumor was designated as, “thymoma with pseudosarcomatous stroma,” [1] or, by analogy with metaplastic carcinoma

of the breast, “low-grade metaplastic carcinoma of the thymus [2].” The term “metaplastic thymoma” was adopted in the WHO classification of thymic tumors subsequent to 2004 [4].

Histologically, metaplastic thymoma is well-circumscribed or encapsulated, lacking the lobulation and fibrous bands of conventional thymomas and demonstrating a distinctive dual population of keratin-positive epithelioid cells in an anastomosing nested pattern and a variably cellular keratin-negative spindle cell component [1, 4–6]. The proportions of epithelioid and spindle cells vary between tumors, and some authors have proposed that the spindled cells represent a reactive stromal component based on their ultrastructural features [1], while others believe that both components are neoplastic based on their immunohistochemical and histologic features [2]. Metaplastic thymoma pursues a benign clinical course, with only rare reports of recurrence or malignant transformation.

The genomic alterations driving metaplastic thymoma have not previously been defined. In this study, we report for the first time recurrent translocation events involving Yes Associated Protein 1 (*YAP1*) and Mastermind Like

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Transcriptional Coactivator 2 (*MAML2*) genes in this tumor type.

## Materials and methods

### Patient selection and histologic evaluation

Paraffin-embedded formalin-fixed metaplastic thymoma tissue was obtained from hospital archives and authors' consultation files following Brigham and Women's Hospital Institutional Review Board approval. These included two cases from the Department of Pathology at Brigham and Women's Hospital and six cases from the Department of Pathology, Queen Elizabeth Hospital, Hong Kong. Samples were acquired over a 21-year period. Demographic, clinical, and follow-up data were abstracted from the medical records and discussion with consulting pathologists.

At least one representative hematoxylin and eosin-stained whole tissue section was examined in each case. Tumors were diagnosed in accordance with the 2015 WHO classification [4].

### Next-generation sequencing

Targeted next-generation sequencing including all exonic regions and selected introns of 447 cancer-associated genes was performed at Brigham and Women's Hospital using OncoPanel (version 3). The target genes are listed in Supplementary Table 1. DNA was isolated from paraffin-embedded formalin-fixed tissue sections. Library preparation, custom hybrid capture (Agilent SureSelect, Agilent Technologies, Santa Clara, CA), and massively parallel sequencing (HiSeq 2500, Illumina, San Diego, CA) were performed as previously described [7, 8].

### RNA sequencing

RNA fusion transcript detection was performed using Anchored Multiplex PCR. Total nucleic acid isolated from formalin-fixed paraffin-embedded tissue sections underwent reverse transcription, second strand synthesis, and adapter-ligation as previously described [9]. Sequencing libraries of targeted genes (Supplementary Table 1) were created using ArcherDx Fusion Plex Solid Tumor Kit (ArcherDx, Boulder, CO) and sequenced on an Illumina NextSeq 2. Fusion calling was performed using a laboratory-developed algorithm.

### Thymic neoplasm data analysis

An institutional instance of cBioPortal [10] housed at the Dana Farber Cancer Institute containing genomic alterations

from over 20,000 de-identified tumors including 52 thymic neoplasms was interrogated for the presence of *YAP1-MAML2* rearrangements.

### G2FT1A mutation analysis

DNA extracted from formalin-fixed paraffin-embedded tissues was subjected to allele-specific real-time polymerase chain reaction to detect *GTF2I* c.74146970T>A (p.L424H). PCR primer and probe sequences for detection of mutant (L424H) are as follows:

*Forward primer* GTF2I-F: 5'-GAT CCC GTA CCC TCT TTT CC-3'.

*Reverse primer* (mutant specific) GTF2I-R2: 5'-AAC GAA TCC TTT CCT TTG TATG-3'.

*Taqman probe* GTF2I-TP4: [FAM] 5'-TAT CCT CTC CAG GCG AGG AAT T-3'[MGB-NFQ].

For control PCR, the forward primer and probe are the same as for L424H PCR, while the reverse primer is as follows:

*Reverse primer* GTF2I-CR: 5'-CAG GAA TCC AAG AGT CTT ACT TC-3'.

## Results

Demographic and clinicopathologic features are summarized in Table 1. Study patients consisted of one man and seven women with a median age of 55 (Q1-Q3: 43–59). The tumors ranged from 2.5 to 8.2 cm in size and presented as incidental imaging findings in five of seven patients. Two additional patients presented with chest pain and mild ocular myasthenia gravis, respectively. Clinical follow-up was available in six patients, all of whom were alive and well at 1–22 years after resection (median 8.25; Q1–Q3: 3.75–9.75). No recurrences, local invasion, or distant metastases were noted in any of the patients.

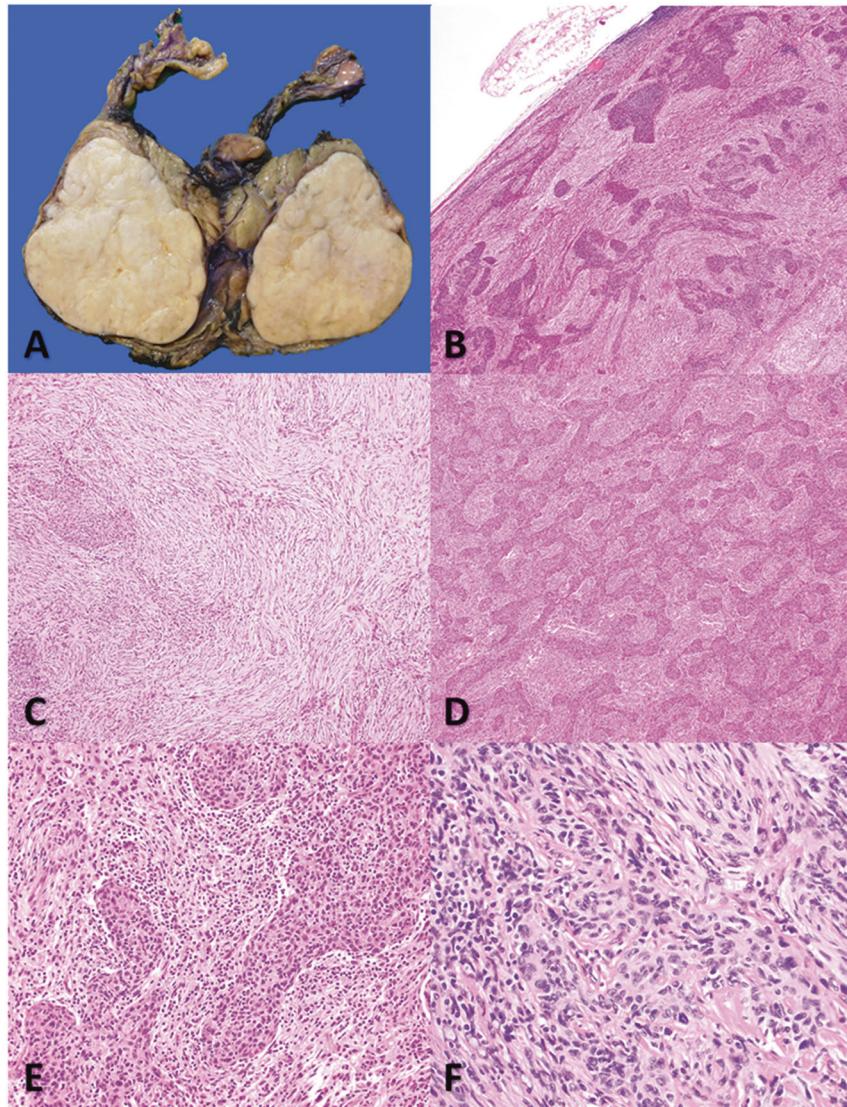
Histologic evaluation revealed circumscribed biphasic tumors consisting of variably sparse to abundant anastomosing nests of epithelioid tumor cells embedded in a cellular stroma characterized by delicately elongate bland-looking spindle cells (Fig. 1). Atypia, including nucleomegaly and hyperchromasia with a smudged chromatin pattern, was frequently present in the epithelioid component; however, mitotic figures were infrequent and necrosis was absent in all cases. Lymphocytes were sparse within the tumors. A compressed rim of normal thymic tissue could often be identified at the periphery.

Archival paraffin-embedded tissue was used for molecular analysis (Table 2). Next-generation sequencing failed in two cases due to poor nucleic acid quality, one each from 1997 and 2008. DNA-based targeted next-generation sequencing identified a rearrangement involving the *YAP1*

**Table 1** Clinical and pathologic characteristics of study cases

Case no.	Sex	Age	Presentation	Tumor size (cm)	Follow-up
1	F	29	Incidental	3.4	A&W at 2.5 years
2	F	66	Not available	2.7	Not available
3	M	57	Incidental	2.5	Not available
4	F	32	Chest pain	8.2	A&W at 7.5 years
5	F	66	Mild ocular myasthenia gravis	7.0	A&W at 9 years
6	F	56	Incidental	7.0	A&W at 22 years
7	F	55	Incidental	7.0	A&W at 10 years
8	F	47	Incidental	7.3	A&W at 1 year

**Fig. 1** **a** Gross image of a metaplastic thymoma with a firm tan-white cut surface and lobulated but well-circumscribed border. **b** Metaplastic thymomas are also microscopically well-circumscribed. This tumor demonstrated numerous irregular nests of epithelioid cells at the periphery of the tumor ( $\times 40$ ), while **c** central areas showed fewer epithelioid nests and a more prominent spindle cell component with a storiform growth pattern ( $\times 100$ ). **d** Metaplastic thymoma with more evenly distributed epithelioid component presenting in an interconnected trabecular pattern ( $\times 40$ ), with **e** a sparse lymphocytic infiltrate in both stromal and epithelioid components ( $\times 200$ ). **f** Nuclear atypia characterized by hyperchromasia, nucleomegaly, and irregular nuclear contours of the epithelioid component was seen in most tumors ( $\times 200$ )



and *MAML2* genes in four tumors (patients 1, 3, 5, and 8). The breakpoint locations (Table 2) occurred in intron 1/exon 2 (cases 3, 5, and 8; Supplementary Fig. 1) and intron 5 (case 1) of *YAPI*. In all four cases the *MAML2* breakpoint mapped to intron 1. In two cases (2 and 4), sequencing was successful, but no fusions or somatic

mutations were detected. Anchored multiplex PCR performed on these two cases identified *YAPI-MAML2* transcripts fusing exon 5 of the *YAPI* gene and exon 2 of the *MAML2* gene resulting from an intrachromosomal inversion event. No other fusion events were detected. In all cases, predicted functional (in-frame) fusion events showed an

**Table 2** Results of genomic analyses

Case no.	GTF2I mutation status	DNA sequencing results		RNA fusions detected	
		YAP1 breakpoint	MAML2 breakpoint	5' partner	3' partner
1	WT	11:102080322 (intron 5)	11:95871814 (intron 1)	–	–
2	WT	None detected	None detected	YAP1 (e5)	MAML2 e2-5
3	WT	11:101982044 (intron 1)	11:95983749 (intron 1)	–	–
4	WT	None detected	None detected	YAP1 (e5)	MAML2 e2-5
5	WT	11:101983520 (intron 1)	11:95952533 (intron 1)	–	–
6	WT	Failed	Failed	–	–
7	WT	Failed	Failed	–	–
8	WT	11:101984883 (exon 2)	11:95856083 (intron 1)	–	–

**Table 3** Previously published clinical features of metaplastic thymoma

Study	n (M:F)	Age range (years)	Size (cm)	Follow-up	Mean follow-up
Suster et al. [1]	6 (4:2)	28–70	6–10	A&W 5–12 years	10 years
Yoneda et al. [2]	5 (4:1)	44–71	8–16	A&W 12–21 months; 1 recurrence at 14 months with death at 6 years	16.4 months
Noh et al. [6]	1 (M)	53	9	N/A	N/A
Jin et al. [5]	3 (0:3)	33–58	4–8	A&W 1 month–9.5 years	5.2 years
Moritani et al. [14]	1 (M)	43	8	Presented with transformation to sarcomatoid carcinoma	N/A
Poorabdollah et al. [3]	1 (M)	61	11	N/A	N/A
Lu et al. [15]	1 (F)	63	18.5	Presented with transformation to sarcomatoid carcinoma	N/A
Liu et al. [17]	7 (2:5)	36–61	5–14	A&W at 11–133 months	82 months
Kang et al. [13] <sup>a</sup>	4 (1:3)	43–56	4–8	A&W at 5–55 months	29 months
Tajima et al. [12] <sup>b</sup>	1 (F)	3.6	N/A	N/A	N/A

<sup>a</sup>One of the four patients had myasthenia gravis<sup>b</sup>Patient presented with myasthenia gravis

orientation of 5' *YAP1* and 3' *MAML2*. Copy number profiling by DNA sequencing showed one copy deletion of the C-terminus of *YAP1* beginning at the predicted breakpoint in five of six cases, providing further support for a rearrangement event. Of note, C-terminus *YAP1* gene deletion was evident by DNA sequencing in one case with a fusion detected only by RNA sequencing. No other recurrent alterations were identified in the cohort. Additional somatic variants were detected in only two cases, including monosomy of chromosomes 13 and 22 as well as truncating mutations in *RSPO2* and *MED12* (case 5); and gain of 5q and deletions on 11q and 18 (case 8).

The genomic profiles of 52 thymic neoplasms previously sequenced by OncoPanel at our institution as part of the PROFILE institutional sequencing initiative were examined for *YAP1-MAML2* rearrangements [11]. The institutional cohort contained 25 thymomas, 25 thymic carcinomas, and 2 thymic neuroendocrine tumors. No fusion events were detected. Expected genomic alterations were observed in

thymic carcinomas including *TP53* mutations in nine (36%) cases and *CDKN2A* deletion in seven (28%) cases. No recurrent pathogenic or likely pathogenic variants were detected in the thymomas.

Allele-specific RT-PCR showed no *GTF2I* c.74146970T>A mutation in any of the tumors.

## Discussion

Metaplastic thymomas are very rare, with only 30 cases reported in the English language literature (Table 3). This study represents the largest case series, with long follow-up information. Combining all available data, the tumor occurs predominantly in middle-aged subjects, with slight female predominance. In contrast to conventional thymomas (type A, AB, B1, B2, or B3), there is a low frequency of association with myasthenia gravis (3 of 38) [12, 13]. The clinical outcome also appears more favorable, with only one

reported recurrence [2]. Although two cases have been reported to show histologic transformation to sarcomatoid carcinoma [14, 15], there is no follow-up information on the consequence of this phenomenon.

Metaplastic thymoma shows highly characteristic morphologic features distinct from conventional thymomas. Furthermore, intratumoral lymphoid cells are generally sparse and are TdT-negative [4], with the exception of one reported case with patchy infiltrates of TdT-positive lymphoid cells and accompanied by myasthenia gravis [12]. The histogenesis and relationship between metaplastic thymoma and other thymic epithelial neoplasms remain unknown. Based on the presence of keratin-negative, EMA-positive spindled cells in a subset of type AB thymomas, Miki et al. have suggested a relationship between metaplastic thymoma and type AB thymoma [16]. A previous study of seven cases demonstrated no gross chromosomal abnormalities by comparative genomic hybridization [17], but comprehensive studies of genetic alterations in metaplastic thymoma to clarify its relationship to other thymic tumors are lacking.

In this study, all six tumors successfully analyzed by sequencing methods demonstrated *YAP1-MAML2* fusions, suggesting a common pathogenetic mechanism. Two distinct products were identified: 5' *YAP1* exon 1 fused to 3' *MAML2* exons 2–5 or 5' *YAP1* exons 1–5 fused to 3' *MAML2* exons 2–5.

*MAML2* is a transcription coactivator that directly binds to notch proteins via its N-terminal basic domain and results in upregulation of notch pathway target genes [18]. Fusions of the *MAML2* gene to the *CRTC1* and *CRTC3* genes are distinctive of mucoepidermoid carcinoma, but have also been described in ovarian cancer cell lines [19–21]. *MLL-MAML2* translocations have been described in acute myelogenous leukemia and myelodysplastic syndrome [22]. In mucoepidermoid carcinoma, *CRTC1-MAML2* fusions involving breakpoints in exons 2–5 of *MAML2* result in a fusion product with a retained *MAML2* transactivation domain [20]. Consequent activation of select notch pathway elements and cAMP/CREB-responsive genes may play a role in malignant transformation [19, 20], although other studies suggest that *MAML2* translocations that do not include the N-terminal basic domain may activate genes unrelated to the notch pathway [18]. *YAP1*, a transcriptional coactivator regulated by the Hippo and Wnt pathways, plays a role in organ growth during normal development, and its overexpression in cancer results in transcriptional activation of proliferation-associated genes that is dependent on its N-terminal TEAD-binding domain [23]. *YAP1* also plays a role in mechanotransduction of cell-extracellular matrix interactions and contact inhibition of cell growth in both cancer cells and cancer-associated fibroblasts [23].

*YAP1-MAML2* rearrangements have recently been described in cell lines of ovarian carcinoma, glioblastoma, tongue squamous cell carcinoma, and rare cases of nasopharyngeal carcinoma. The gene fusion yields a fusion protein that acts via a TEAD1-dependent mechanism to generate a *YAP1*-associated transcriptional signature and thereby promote tumor cell growth [24]. Recently, RNA sequencing studies of poroma, a benign skin tumor, and porocarcinoma, its malignant counterpart, identified *YAP1-MAML2* fusions in 71 of 104 (68%) poromas and 1 of 11 (9%) of porocarcinomas [25]. As in our study, a variant *YAP1* breakpoint occurring in intron 1 was also detected in over 15% of poromas tested. The *YAP1* TEAD-binding domain is encoded by exon 1 and therefore is conserved even when the breakpoint falls in intron 1. Sekine et al. confirmed that both the *YAP1(e5)-MAML2* and *YAP1(e1)-MAML2* fusions upregulate TEAD-dependent transcription in *in vitro* studies [25].

Review of our DNA panel sequencing coverage showed limited capture of intronic regions in introns 5 and 6 of *YAP1*; this likely explains the inability of OncoPanel to detect fusions in the two cases with confirmed fusions by RNA sequencing. The limited sensitivity of DNA-based sequencing for rearrangement events has been well-documented [26, 27]. The use of DNA-based sequencing is a limitation of our institutional analysis of thymic neoplasms and leaves open the possibility that similar fusions have gone undetected historically. However, *YAP1-MAML2* fusions in thymomas or thymic carcinomas have also not been reported in the literature despite several major efforts to genetically characterize thymic neoplasms [28, 29].

GTF2I c.74146970T>A (p.L424H) mutation occurs at a high frequency in type A and type AB thymomas (79–87%) and a low frequency in type B thymomas (0–32%) [28–30]. The molecular findings of the specific *YAP1-MAML2* fusions and lack of GTF2I L424H mutation provide a strong support that metaplastic thymoma is distinct from conventional thymomas (types A, AB, B1, B2, and B3). *YAP1-MAML2* fusion likely represents a driver of neoplasia. Our findings therefore support classification of metaplastic thymoma separate from other thymomas, as an indolent tumor with excellent prognosis that can be diagnosed on morphologic grounds.

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## Compliance with ethical standards

**Conflict of interest** MV performs consulting work for Merck Pharmaceuticals. These disclosures do not apply to the current study, which is not associated with a specific source of funding. LMS reports

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