Review Article

Genomic insights into molecular profiling of thymic carcinoma: a narrative review

So Takata

Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
Correspondence to: So Takata, MD, PhD. Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, 565-0871 Suita, Osaka, Japan. Email: sotakata@imed3.med.osaka-u.ac.jp.

Background and Objective: Thymic carcinoma is an exceptionally rare cancer, with an annual incidence of just 0.15–0.29 per 100,000 people. Owing to its rarity, only few proven treatments have been developed. Understanding its genetic profile is crucial for the development of targeted therapies. However, limited studies have exclusively examined thymic carcinoma mutations, with most investigation combining thymomas and thymic carcinomas. This paper reviews findings from genetic studies focusing on thymic carcinoma alone and compares them to those of thymoma.

Methods: We conducted a PubMed search for relevant English studies on thymic carcinoma genomics. Then, key papers utilizing target sequencing or whole-exome sequencing were analyzed.

Key Content and Findings: The most frequently mutated genes were *TP53*, *CDKN2A*, *CDKN2B*, *CYLD*, *KIT*, *TET2*, *SETD2*, *BAP1*, and *ASXL1*. *TP53* and *CDKN2A* are correlated with poor prognosis. *CYLD*, which regulates signaling related with proliferation and interacts with AIRE expression and T cell development, might predict the immunotherapy response. *KIT* mutations might enable targeted therapy. *TET2*, *SETD2*, *BAP1*, and *ASXL1* regulate epigenetics, suggesting disruption of these mechanisms. Higher tumor mutational burden (TMB) and 16q loss distinguish thymic carcinoma from thymoma. Although some copy number aberrations are shared, thymic carcinoma exhibits a mutational profile distinct from that of thymoma.

Conclusions: Thymic carcinoma demonstrates a unique genomic landscape, suggesting a molecular pathogenesis distinct from that of thymoma. Our findings revealed prognostic biomarkers such as *TP53*/*CDKN2A* and potential therapeutic targets such as *KIT*. Because thymic carcinoma is extremely rare, sharing molecular profiling data could provide valuable insights into the molecular mechanisms driving the development of these tumors.

Keywords: Thymic carcinoma; genomics; mutation; copy number aberration

Received: 10 January 2024; Accepted: 10 April 2024; Published online: 05 June 2024.
doi: 10.21037/med-24-5
View this article at: https://dx.doi.org/10.21037/med-24-5

Introduction

Background

Thymic carcinoma is a rare form of thymic epithelial tumor originating in the thymus. The overall incidence of thymic carcinoma in Japan is 0.15–0.29 per 100,000 person-years (1,2). Owing to its rarity, evidence-based treatments are limited. Notably, approximately around half of the patients with thymic carcinoma patients are unsuitable candidates for surgery (2,3), emphasizing the importance of exploring their genomic profile is crucial for an internal medicine approach.

Regarding treatment, multi-target tyrosine kinase inhibitors (TKIs) and immune checkpoint blockade (ICB) have been one of the treatment options. Sunitinib and lenvatinib showed response rates of 26% and 38% respectively in thymic carcinomas. ICB showed durable responses in 20–25% of patients with thymic carcinoma

Table 1 The search strategy summary

Items	Specification
Date of search	2023/6/1 to 2023/7/1
Databases and other sources searched	PubMed and Web of Science
Search terms used	Thymus and thymic
Timeframe	1982–2023
Inclusion criteria	Original article and review article regarding the genomic features of thymic carcinoma published in English
Selection process	S.T. did the search and selected the manuscript

(4-6). Also, several trials of combination of TKI and chemotherapy or ICB are ongoing (4,7). The reports for genomic findings of thymic carcinoma aimed at elucidating novel therapeutic targets and biomarkers predictive of response are limited.

Rationale and knowledge gap

Although thymic carcinoma is typically classified as a thymic epithelial tumor, Radovich *et al.* proposed it as a distinct entity of thymic epithelial tumors (8). Numerous studies have examined genomic alterations in thymic tumors, including both thymomas and thymic carcinomas. However, only a few studies have specifically focused on thymic carcinoma, owing to its uncommon nature. Therefore, our search was focused on the genomic profiles of thymic carcinoma. Furthermore, genomic findings varied depending on whether targeted or whole-exome sequencing was used.

Objective

Our objective was to provide comprehensive summary of the genomic discoveries related to thymic carcinoma. I present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-5/rc).

Methods

We systematically searched for relevant studies published on PubMed from 1982 to 2023, utilizing various combinations of the terms “thymic” and “thymus”. Articles related to genomics were selected by reviewing abstracts. Additional papers were identified by checking cited references and examining reference lists. Publications published in languages other than English were excluded. Data extraction was performed based on their relevance to the topic. Additional details of this method are presented in *Table 1*.

Results

Recurrent mutations

The most frequently mutated genes depend on the panel list of target genes, and these recurrent mutations are detailed in *Table 2*.

The results of whole-exome sequencing vary across different reports. Subsequently, recurrently reported mutations were focused. The most frequently reported genes were *TP53*, *CDKN2A*, *CDKN2B*, *CYLD*, *KIT*, *TET2*, *SETD2*, *BAP1*, *ASXL1* and *FGFR3* (*Table 2*). The pathological finding of immunohistochemical staining for TP53 was strongly correlated with *TP53* mutations in patients with thymic carcinoma, similar to observations in other cancer types (30), and *TP53* mutations were associated with poor prognosis (16). Cyclin dependent factor such as *CDKN2A* and *CDKN2B* were also frequently reported genes. Particularly, loss of $p16^{INK4A}$ (encoded by *CDKN2A*) expression due to a homozygous *CDKN2A* deletion was confirmed to be correlated with a worse prognosis, including earlier recurrence and shorter overall survival (31). Both *TP53* and *CDKN2A* are recurrently mutated and have been confirmed to be associated with poor prognosis. CYLD is a deubiquitinating enzyme, that regulates cell signaling pathways (32). COSMIC, the Catalogue of Somatic Mutations in Cancer, explain that *CYLD* gene role as tumor suppressor gene according to its multiple role such as regulator of multiple pathway involving EGFR pathway. CYLD is related with angiogenesis (33), which is one of central pathways of thymic carcinoma (7). In addition, its

Table 2 Genomic profiling of thymic carcinoma patients

Report No.	Method	Number*	Histological subtype [number of patients]	Genetic variations in each subtype	Number of target genes	Mutation [number of patients]	Country	Sample	Authors	Year
1	WES	10, 0	Sq [9], Undif [1]	Accessible	–	*TET2* [3], *ARID1B* [2], *CYLD* [2], *SETD2* [2]	Japan	FF	Saito *et al.* (9)	2017
2	WES	9, 1	Sq [4], Undif [4], LCNEC [1], unknown [1]	Accessible	–	*TP53* [1], *NRAS* [1]	USA	FF	Radovich *et al.* (8)	2018
3	WES	19 (TC)	–	No	–	*KMT2C* [2], *CYLD* [2], *NCOA1* [2], *NOTCH1* [2], *NSD1* [2], *WHSC1L1* [2]	China	FF	Fang *et al.* (10)	2021
4	WES	9 (TC)	–	No	–	*MYO16* [3]	China	FFPE	Yang *et al.* (11)	2023
5	WES & TS	16 (TC)	Sq [5], Undif [6], NEC [1], unknown [4]	No	197	*TP53* [4], *CYLD* [3], *BAP1* [2], *PBRM* [2], *CDKN2A* [2]	USA	FF and FFPE	Petrini *et al.* (12)	2014
6	WES & TS	11 (TC)	–	No	–	*CYLD* [3], *TP53* [2]	USA	No information	Ardeshir-Larijani *et al.* (13)	2023
7	TS	42, 5	–	No	197	*TP53* [12], *BAP1* [6], *CYLD* [4], *KIT* [4], *DNMT3A* [4], *SETD2* [4], *TET3* [6.4%]	USA	FFPE	Wang *et al.* (14)	2014
8	TS	12, 0	Sq [12]	No	409	*NF1* [2]	Japan	FF	Shitara *et al.* (15)	2014
9	TS	15 (TC)	Sq [14], Undif [1]	No	275	*TP53* [4], *KDM6A* [3], *SMAD4* [2], *CYLD* [2], *SETD2* [2], *KMT2C* [2], *KMT2D* [2]	USA	FF and FFPE	Moreira *et al.* (16)	2015
10	TS	15 (TC)		No	22	*PIK3CA* [2]	China	FFPE	Song *et al.* (17)	2016
11	TS	52[§]	Sq [47], Ad [2], SCC [1], poorly differentiated carcinoma [7], NOS [7]	No	50	*TP53* [4], *KRAS* [2]	Japan	FF and FFPE	Asao *et al.* (18)	2016
12	TS	34, 1	Sq [34], LEL [1]	No	50	*TP53* [9], *CDKN2A* [4], *FGFR3* [2], *KIT* [2]	Austria	FFPE	Enkner *et al.* (19)	2017
13	TS	5 (TC)	–	No	315	*KMT2C* [5], *ARID1A* [5], *MAP3K1* [5]	China	No information	Chen *et al.* (20)	2020
14	TS	15, 0	Sq [6], LEL [3], Ad [2], basaloid [4]	Accessible	50	*FGFR3* [5], CDKN2A [3], *SMARCB1* [2]	Italy	FFPE	Asselta *et al.* (21)	2021
15	TS	48, 6	Sq [44], Ad [4], carcinoid [5], LCNEC [1]	Accessible	50	*TP53* [12], *KIT* [4], *PDGFRA* [3], *PIK3CA* [3], *EGFR* [2], *KRAS* [2], *FBXW* [2], *VHL* [2]	Japan	FFPE	Sakane *et al.* (22)	2021
16	TS	15, 4	Sq [10], LEL [1], Ad [1], unknown [3], carcinoid [2], SCC [1], undefined [1]	Accessible	450	TC: *CDKN2A* [9], *CYLD* [6], *CDKN2B* [5], *TP53* [4] TNET: *MEN1* [2]	China	FFPE	Wang *et al.* (23)	2021
17	TS	28, 6	Sq [23], basaloid [1], Ad [1], Muco [1], NUT [1], LCNEC [6], NOS [1]	No	15	*TP53* [8], *KIT* [2], *ERBB2* [2]	Poland	FFPE	Szpechcinski *et al.* (24)	2022

Table 2 *(continued)*

Table 2 *(continued)*

Report No.	Method	Number*	Histological subtype [number of patients]	Genetic variations in each subtype	Number of target genes	Mutation [number of patients]	Country	Sample	Authors	Year
18	TS	174	Sq [69], Undif [54], NEC [30], LEL [5], basaloid [5], Ad [7], sarcomatoid [4]	Accessible	315	*CDKN2A* [65], *CDKN2B* [45], *TP53* [44], *CYLD* [19], *KIT* [15], *BAP1* [13]	USA	FFPE	Girard *et al.* (25)	2022
19	TS	8, 0	Sq [5], Ad [3]	No	315	*KMT2C* [5], *NFKBIA* [3], *TET2* [3], *TP53* [2], *RPTOR* [2], *ASXL1* [2], *BRCA2* [2]	China	FFPE	Tan *et al.* (26)	2023
20	TS	414 (FMI), 52 (CCAT)	–	No	324	FMI: *CDKN2A* [165], *TP53* [125], *CDKN2B* [102], *BAP1* [34], *TET2* [33], *KIT* [33], *SETD2* [32], *NFKBIA* [32], *ASXL1* [29], *KMT2D* [25] C-CAT: *CDKN2A* [20], *TP53* [19], *CDKN2B* [16], *KMT2D* [12], *MTAP* [12], *NFKBIA* [11]	USA and Japan	FFPE	Kurokawa *et al.* (27)	2023
21	Other†	7, 0	Sq [7]	No	12	*KIT* [2], *KRAS* [1]	USA	FF	Girard *et al.* (28)	2009
22	Other‡	48, 6	Sq [44], Ad [4], carcinoid [5], LCNEC [1]	Accessible	6	*KRAS* [6], *HRAS* [3], *TP53* [5]	Japan	FFPE	Sakane *et al.* (29)	2019

Listed with a frequency more than 5% in each cohort. *, the number of patients with thymic carcinoma and thymic neuroendocrine tumor were described respectively; †, array-based comparative genomic hybridization; ‡, single-base extension multiplex assay; §, total patients number was 64, of which 52 patients were analyzed for genetic testing. WES, whole exome sequencing; TS, target sequencing; FMI, Foundation Medicine Inc.; CCAT, Center for Cancer Genomics and Advanced Therapeutics; Sq, squamous; Undif, undifferentiated carcinoma; LCNEC, large cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; Ad, adenocarcinoma; SCC, small cell carcinoma; Muco, mucoepidermoid carcinoma; NOS, not otherwise specified; LEL, lympho-epithelial carcinoma; NUT, NUT carcinoma; C-CAT, Center for Cancer Genomics and Advanced Therapeutics; FF, fresh frozen; FFPE, formalin-fixed paraffin-embedded; TC, thymic carcinoma; TNET, thymic neuroendocrine tumor.

position locates in chromosome 16q, of which copy number loss is characteristic to thymic carcinoma (8). Additionally, it is related with differentiation and maturation of medullary thymic epithelial cells and the regulation of AIRE expression, essential for T cell development (34). The reported frequency of truncating mutations in *CYLD* in patients with thymic carcinoma through whole exome sequencing suggesting that loss of function of *CYLD* can influence tumorigenesis. Moreover, *CYLD* mutations can serve as candidate biomarkers for the response to ICB. In a small phase 2 study using pembrolizumab in thymic carcinoma patients, the responder group had a higher ratio of *CYLD* mutations than the non-responder group (35). This result may be related to the upregulation of PD-L1 expression via interferon gamma, resulting in the down-regulation of *CYLD in vitro* (36). In contrast, target sequencing did not reveal many *CYLD* mutations, as shown in *Table 2*. This is because CYLD is not included in the many of the panel lists of mutations. Further, *KIT* mutations are one of the druggable mutations. Buti *et al.* reported a patient with thymic carcinoma harboring *KIT* mutation showed an impressive response to imatinib treatment (37). Although two related small phase 2 studies using imatinib reported no response in patients with unselected thymic epithelial tumors (and possibly wild-type cKIT) (38), targeted therapy can be one of the treatment options for patients with thymic carcinoma who have *KIT* mutations. *TET2* mutation is mainly reported by Saito *et al.* (9). They identified three mutations in ten Japanese patients with thymic carcinoma. *TET2* affects DNA demethylation by converting 5methylcytosine to 5-hydroxymethylcytosine, resulting in abnormal genomic hypermethylation and

reduced repression of hypermethylated genes in acute myeloid leukemia (39). The author further analyzed the methylation status using the bead array method and emphasized the difference in the methylation status of *TET2* mutation-positive and *TET2* mutation-negative patients. Another group identified recurrent mutations in histone modification-related genes, such as *SETD2*, *BAP1*, and *ASXL1*. The authors suggested that a possible disruption of epigenetic regulation in thymic carcinoma, which is a characteristic of genome that differs from that of thymoma. Additionally, several epigenomic alteration of thymic carcinoma has been found, for example, abnormal methylation of *KSR1*, *ELF3*, *IL1RN*, and *RAG1* (40). *FGFR3 mutations* were found (26.6%) in four patients with thymic carcinoma in the report of Asselta *et al.* Also, the patients with *FGFR3* mutations conferred a statistically significant survival advantage in addition to the lower proliferation fraction using Ki-67 estimation. Dysregulation of the FGFR signaling pathway through genetic alterations in FGFR2/3 is implicated in driving carcinogenesis across various solid tumor types (21).

Because most of thymic carcinoma is squamous cell carcinoma, these recurrent genomic finding could be regarded as the characteristics of squamous cell carcinoma of thymus. Its rarity of other subtypes led disability of finding recurrent mutations in another subtypes. Thereafter focusing on unique mutation even if found in a few patients, two basaloid and one lymphoepithelioma-like carcinoma harbored *FGFR3* mutations, and a patient with adenocarcinoma intriguingly uniquely had *APC* out of frame deletion (21).

Mutations in thymic carcinoma compared to thymoma

The largest cohort study on target sequencing of thymic epithelial tumors suggested that *CDKN2A*, *CDKN2B* and *TP53* were more frequently altered in patients with thymic carcinoma than in those with thymoma (27). Additionally, *SETD2* mutations were common in both groups, which is consistent with another cohort study findings (14). Notably, *CYLD* mutation was specific to thymic carcinoma (12,14). Although this finding is intriguing, validation is required because the gene panel lists used in many other studies do not include the *CYLD* gene. Therefore, further analysis of large-scale cohorts is necessary. Regarding *KIT* mutations, a few thymic carcinoma patients had that, and one patient harbor pathogenic *KIT* p.(Leu576Pro) variant. Although a few thymoma patients had *KIT* mutations, they were considered variants of unknown significance, different from those observed in patients with thymic carcinoma (24). *TET2* mutations, emphasized by Saito *et al.* (9), were also unique to patients with thymic carcinoma in a study by Tan *et al.* (thymic carcinoma 3/8; thymoma 0/39) (26). *BAP1* mutations were slightly more common in patients with thymic carcinoma; however, they were also observed in some thymoma patients (12,14). *ASXL1* mutations were recurrent but not frequently enough to be evaluated.

Tumor mutational burden (TMB) and microsatellite instability (MSI) status

TMB is higher in thymic carcinomas than in thymic tumors, as indicated in several reports (8,25,27). However, thymic carcinomas exhibit elevated TMB compared to thymomas (8), accounting for 6–7% of cases (15,20). In addition, although few reports on MSI status are limited, the two largest studies utilizing target-sequencing indicate that high MSI cases are rare, ranging from 0–2.3% (25,27). Because of its rarity, it remains unclear whether the incidence of immune-related adverse events (irAEs) from ICB treatment is higher among thymic carcinoma patients compared to those with other solid tumors. Meanwhile, irAEs by using ICB for thymoma patients has reported clearly more frequently than individuals with other solid tumors (21). ICB can be a treatment option for patients with thymic carcinoma, although careful judgment is essential as a problem specific to immune organ (41).

Shared and divergent of copy number variations of thymic carcinoma and thymoma

The Cancer Genome Atlas (TCGA) project revealed that chromosome 16q loss is more common in thymic carcinoma than in thymoma (8). They estimated arm and focal-level copy number aberrations in 117 thymic epithelial tumor samples (107 thymomas and 10 thymic carcinomas). Also, chromosome 1q amplification and chromosome 6p and 6q loss were common in both thymic carcinomas and thymomas. This observation, consistent with prior report (42), has led to the hypothesis that thymomas (especially type B3 thymomas) and thymic carcinomas may represent sequential pathologies. However, the validity of this hypothesis remains unclear. The TCGA study revealed thymic carcinoma as distinct group with respect to molecular pathogenesis, based on multiomics analysis involving whole-exome sequencing. The assertion

is further supported by the detection of only two cases of combined thymic carcinoma and B3 thymomas among a substantial cohort of more than 600 thymomas, inclusive of type B2 and B3 thymomas (43). However, this concept does not entirely exclude the possibility of malignant transformation from thymoma to thymic carcinoma. Thymic carcinoma typically develops de novo, the copy number aberrations observed in thymic squamous tumors differ from those in squamous cells of other organs such as lung cancer (28), Despite these characteristics, given that thymoma and thymic carcinoma share chromosome 1q amplification and chromosome 6 loss, the possibility of thymoma rarely transforming in thymic carcinoma persists. Unlike the mixed types, there are reports of two cases that were diagnosed as thymoma at the time of initial diagnosis and were diagnosed as thymic carcinoma after a period of time (15 and 40 years later) (44,45). The transformation is challenging to study because of its rarity, however, it can be revealed by genomic profiling of heterochronic samples from the same patient who showed transformation from thymoma to thymic carcinoma.

Mutational signature

Saito *et al.* (9) reported mutational signatures in all analyzed patients with thymic carcinoma. The majority group, consisted of 8 out of 10 instances, exhibited primarily COSMIC signature 1 (clock-like, http://cancer.sanger.ac.uk/cosmic/signatures), associated with the spontaneous deamination of 5-methylcytosine. However, two cases stood out in the minority group, displaying COSMIC signatures 5 (clock-like) and 6 (DNA mismatch repair deficit). Additionally, a patient with TCGA referral demonstrated an unusually high TMB, showcasing a mutational pattern similar to COSMIC signature 6. This patient presented a pathogenic nonsense mutation of *MLH1*, accompanied by a lack of its expression.

Conclusions

Thymic carcinomas have unique genomic profiles compared to thymomas, however, they share certain copy number aberrations. These mutations may present novel targets for therapeutic approaches.

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.
Funding: This work was supported by the Japan Society for the Promotion of Science KAKENHI (23K19534) and the Osaka Medical Research Foundation for Intractable Diseases (29-1-23).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Masatsugu Hamaji) for the series "Locally Advanced Thymic Epithelial Tumors" published in *Mediastinum*. The article has undergone external peer review.

Reporting Checklist: The author has completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-24-5/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-24-5/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-24-5/coif). The series "Locally Advanced Thymic Epithelial Tumors" was commissioned by the editorial office without any funding or sponsorship. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and

associations with subsequent malignancies. Int J Cancer 2003;105:546-51.
2. Koizumi T, Otsuki K, Tanaka Y, et al. National incidence and initial therapy for thymic carcinoma in Japan: based on analysis of hospital-based cancer registry data, 2009-2015. Jpn J Clin Oncol 2020;50:434-9.
3. Uramoto H, Takiguchi T, Koizumi T, et al. Multi-institutional survey of thymic carcinoma patients in Hokushin region. J Cancer Res Clin Oncol 2022;148:419-24.
4. Conforti F, Pala L, De Pas T, et al. Investigational drugs for the treatment of thymic cancer: a focus on phase 1 and 2 clinical trials. Expert Opin Investig Drugs 2022;31:895-904.
5. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. Lancet Oncol 2020;21:843-50.
6. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol 2015;16:177-86.
7. Tateo V, Manuzzi L, Parisi C, et al. An Overview on Molecular Characterization of Thymic Tumors: Old and New Targets for Clinical Advances. Pharmaceuticals (Basel) 2021;14:316.
8. Radovich M, Pickering CR, Felau I, et al. The Integrated Genomic Landscape of Thymic Epithelial Tumors. Cancer Cell 2018;33:244-258.e10.
9. Saito M, Fujiwara Y, Asao T, et al. The genomic and epigenomic landscape in thymic carcinoma. Carcinogenesis 2017;38:1084-91.
10. Fang W, Wu CH, Sun QL, et al. Novel Tumor-Specific Antigens for Immunotherapy Identified From Multi-omics Profiling in Thymic Carcinomas. Front Immunol 2021;12:748820.
11. Yang J, Zhang B, Guan W, et al. Molecular genetic characteristics of thymic epithelial tumors with distinct histological subtypes. Cancer Med 2023;12:10575-86.
12. Petrini I, Meltzer PS, Kim IK, et al. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet 2014;46:844-9.
13. Ardeshir-Larijani F, Schneider BP, Althouse SK, et al. Clinicogenomic Landscape of Metastatic Thymic Epithelial Tumors. JCO Precis Oncol 2023;7:e2200465.
14. Wang Y, Thomas A, Lau C, et al. Mutations of epigenetic regulatory genes are common in thymic carcinomas. Sci Rep 2014;4:7336.
15. Shitara M, Okuda K, Suzuki A, et al. Genetic profiling of thymic carcinoma using targeted next-generation sequencing. Lung Cancer 2014;86:174-9.
16. Moreira AL, Won HH, McMillan R, et al. Massively parallel sequencing identifies recurrent mutations in TP53 in thymic carcinoma associated with poor prognosis. J Thorac Oncol 2015;10:373-80.
17. Song Z, Yu X, Zhang Y. Rare frequency of gene variation and survival analysis in thymic epithelial tumors. Onco Targets Ther 2016;9:6337-42.
18. Asao T, Fujiwara Y, Sunami K, et al. Medical treatment involving investigational drugs and genetic profile of thymic carcinoma. Lung Cancer 2016;93:77-81.
19. Enkner F, Pichlhöfer B, Zaharie AT, et al. Molecular Profiling of Thymoma and Thymic Carcinoma: Genetic Differences and Potential Novel Therapeutic Targets. Pathol Oncol Res 2017;23:551-64.
20. Chen K, Che J, Zhang X, et al. Next-generation sequencing in thymic epithelial tumors uncovered novel genomic aberration sites and strong correlation between TMB and MSH6 single nucleotide variations. Cancer Lett 2020;476:75-86.
21. Asselta R, Di Tommaso L, Perrino M, et al. Mutation profile and immunoscore signature in thymic carcinomas: An exploratory study and review of the literature. Thorac Cancer 2021;12:1271-8.
22. Sakane T, Sakamoto Y, Masaki A, et al. Mutation Profile of Thymic Carcinoma and Thymic Neuroendocrine Tumor by Targeted Next-generation Sequencing. Clin Lung Cancer 2021;22:92-99.e4.
23. Wang H, Xu X, Luo L, et al. Mutational landscape of thymic epithelial tumors in a Chinese population: insights into potential clinical implications. Gland Surg 2021;10:1410-7.
24. Szpechcinski A, Szolkowska M, Winiarski S, et al. Targeted Next-Generation Sequencing of Thymic Epithelial Tumours Revealed Pathogenic Variants in KIT, ERBB2, KRAS, and TP53 in 30% of Thymic Carcinomas. Cancers (Basel) 2022;14:3388.
25. Girard N, Basse C, Schrock A, et al. Comprehensive Genomic Profiling of 274 Thymic Epithelial Tumors Unveils Oncogenic Pathways and Predictive Biomarkers. Oncologist 2022;27:919-29.
26. Tan S, Chen J, Wang Z, et al. Genomic characterization of thymic epithelial tumors reveals critical genes underlying tumorigenesis and poor prognosis. Clin Genet 2023;103:529-39.
27. Kurokawa K, Shukuya T, Greenstein RA, et al. Genomic characterization of thymic epithelial tumors in a real-world

dataset. ESMO Open 2023;8:101627.
28. Girard N, Shen R, Guo T, et al. Comprehensive genomic analysis reveals clinically relevant molecular distinctions between thymic carcinomas and thymomas. Clin Cancer Res 2009;15:6790-9.
29. Sakane T, Murase T, Okuda K, et al. A mutation analysis of the EGFR pathway genes, RAS, EGFR, PIK3CA, AKT1 and BRAF, and TP53 gene in thymic carcinoma and thymoma type A/B3. Histopathology 2019;75:755-66.
30. Yemelyanova A, Vang R, Kshirsagar M, et al. Immunohistochemical staining patterns of p53 can serve as a surrogate marker for TP53 mutations in ovarian carcinoma: an immunohistochemical and nucleotide sequencing analysis. Mod Pathol 2011;24:1248-53.
31. Aesif SW, Aubry MC, Yi ES, et al. Loss of p16(INK4A) Expression and Homozygous CDKN2A Deletion Are Associated with Worse Outcome and Younger Age in Thymic Carcinomas. J Thorac Oncol 2017;12:860-71.
32. Marín-Rubio JL, Raote I, Inns J, et al. CYLD in health and disease. Dis Model Mech 2023;16:dmm050093.
33. Alameda JP, Moreno-Maldonado R, Navarro M, et al. An inactivating CYLD mutation promotes skin tumor progression by conferring enhanced proliferative, survival and angiogenic properties to epidermal cancer cells. Oncogene 2010;29:6522-32.
34. Reissig S, Hövelmeyer N, Tang Y, et al. The deubiquitinating enzyme CYLD regulates the differentiation and maturation of thymic medullary epithelial cells. Immunol Cell Biol 2015;93:558-66.
35. He Y, Ramesh A, Gusev Y, et al. Molecular predictors of response to pembrolizumab in thymic carcinoma. Cell Rep Med 2021;2:100392.
36. Umemura S, Zhu J, Chahine JJ, et al. Downregulation of CYLD promotes IFN-γ mediated PD-L1 expression in thymic epithelial tumors. Lung Cancer 2020;147:221-8.
37. Buti S, Donini M, Sergio P, et al. Impressive response with imatinib in a heavily pretreated patient with metastatic c-KIT mutated thymic carcinoma. J Clin Oncol 2011;29:e803-5.
38. Conforti F, Pala L, Giaccone G, et al. Thymic epithelial tumors: From biology to treatment. Cancer Treat Rev 2020;86:102014.
39. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell 2010;18:553-67.
40. Nicolì V, Coppedè F. Epigenetics of Thymic Epithelial Tumors. Cancers (Basel) 2023;15:360.
41. Maniar R, Loehrer PJ Sr. Understanding the landscape of immunotherapy in thymic epithelial tumors. Cancer 2023;129:1162-72.
42. Kelly RJ, Petrini I, Rajan A, et al. Thymic malignancies: from clinical management to targeted therapies. J Clin Oncol 2011;29:4820-7.
43. Marx A, Chan JKC, Chalabreysse L, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? J Thorac Oncol 2022;17:200-13.
44. Wagner KB, Khan A, Mir R, et al. Thymic carcinoma arising from long standing thymoma and presenting with pituitary metastases. Comput Med Imaging Graph 1991;15:411-4.
45. Ohue Y, Matsuoka S, Kumeda H, et al. Development of combined thymic carcinoma and thymoma in an extrathymic lesion during long follow-up for recurrent thymoma. Mol Clin Oncol 2016;4:139-42.

doi: 10.21037/med-24-5
Cite this article as: Takata S. Genomic insights into molecular profiling of thymic carcinoma: a narrative review. Mediastinum 2024;8:39.