Editorial

Differences and similarities of *GTF2I* mutated thymomas in different Eurasian ethnic groups

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Thymic malignancies are rare diseases. They consist mainly of thymomas, carcinomas and neuroendocrine neoplasms. While we commented on the latter entities recently (1,2), we here address the present article of Shimada *et al.* on thymomas (3).

The vast majority of mutational burden in thymoma is related to the general transcription factor II-i (*GTF2I*) gene. In 2014, Petrini *et al.* (4) reported a missense mutation (chr7: 74146970 T>A) of *GTF2I* in 82% in World Health Organization (WHO) type A and in 74% in WHO type AB thymomas. This mutation is exclusively found in thymic epithelial tumors (TETs).

Some confusion exists on the position of the thymine-to-adenine exchange (5): Commonly used labeling for the position is p.L383H (5), p.L404H (6-8), and p.L424H (3,9-12). This is explained by different isoforms of the gene, that comprise slight differences in length and sequence. The predominant isoforms are *GTF2I* β (NM_033000.2) and *GTF2I* δ (NM_001518.3), leading to the protein annotations p.Leu404His and p.Leu383His, respectively (4). However, when using the standard isoform (NM_032999.4) according to the "The Matched Annotation from the NCBI and EMBL-EBI" program (the National Center for Biotechnology Information and Europäisches Laboratorium für Molekularbiologie - European Bioinformatics Institute program) (MANE select, 11) the same mutation would be annotated as p.Leu424His. This issue highlights the importance of stating the isoform specific ID when annotating a mutation on protein or RNA level.

Interestingly, other diseases related to this gene are the inherited Williams-Beuren syndrome, a heterozygous partial microdeletion of chromosome 7q11.23, which amongst many others is characterized by considerable strength in expressive language and a good sense of rhythm; and on the other hand the Somerville-van der Aa syndrome, caused by a chromosome 7q11.23 duplication, whose manifold symptoms include a severe delay in speech and language skills (13,14). Yet, both diseases are not related to thymic abnormalities.

Shimada *et al.* (3) explored the genetic and clinical characteristics of TETs in a Japanese population. The study was conducted between 2013 and 2019. We would like to place the recent article in the current state of knowledge, setting a focus on thymomas and *GTF2I* mutations. Comparable retrospective publications exist from other Eurasian regions—China, India, and Germany (6,12). A summary of the interethnic results can be found in *Table 1*.

The Japanese group is the smallest with 31 patients, but the only prospective. The female to male ratio of 2:1 is in contrast to the reported more or less equal sex distribution in other series. Shimada *et al.* report 38.7% of *GTF2I*

Table 1 Clinical and pathological characteristics in different ethnic groups of TETs (3,6,12)

Characteristics	German (n=77)	Indian (n=37)	Chinese (n=296)	Japanese (n=31)
Sex, n (%)				
Female	33 (42.9)	19 (51.4)	133 (44.9)	21 (67.7)
Male	44 (57.1)	18 (48.6)	163 (55.1)	10 (32.3)
Myasthenia gravis, n (%)*				
No	13 (52.0)	3 (17.6)	279 (94.3)	22 (77.5)
Yes	12 (48.0)	14 (82.4)	17 (5.7)	7 (22.5)
Masaoka-Koga stage, n (%)*				
I	16 (20.8)	24 (64.9)	189 (63.9)	12 (38.7)
II	38 (49.4)	9 (24.3)	40 (13.5)	10 (32.3)
III/IV	23 (29.9)	4 (10.8)	67 (22.6)	9 (29.0)
GTF2I status, n (%)*				
Wildtype	28 (36.4)	12 (35.3)	172 (58.1)	19 (61.3)
p.L424H	9 (63.6)	22 (64.7)	124 (41.9)	12 (38.7)
Histological type, n (%)				
A	15 (19.5)	8 (21.6)	23 (7.8)	1 (3.2)
AB	31 (40.3)	21 (56.8)	89 (30.1)	11 (35.5)
Atypical A/AB	15 (19.5)	2 (5.4)	Not mentioned	Not mentioned
B	16 (20.8)	6 (16.2)	145 (49.0)	17 (54.8)
Carcinoma, n (%)	Excluded	Excluded	39 (13.2)	2 (6.5)
Median age, years	65	50	49	63

*, data in some patients missing, therefore n is lower than in the entire cohort. TETs, thymic epithelial tumors; *GTF2I*, general transcription factor II-i.

mutated thymoma in their series, reflecting the lowest rate amongst the groups. This correlates with the lowest proportion of type A or AB thymoma (38.7%). The Chinese series reports comparable results, whereas in the Indian and German cohorts, a mutation was confirmed in 64%.

It should be noted that thymic carcinomas were excluded in the German/Indian comparison group, but included in the Chinese and Japanese. Thymic carcinomas only rarely show *GTF2I* mutations.

The incidence of myasthenia gravis, a condition commonly associated with TETs and found in 22% of the Japanese patients, varied grossly in the groups, ranging from 5.7% in the Chinese to 82.4% in the Indian data.

So, concluding the Japanese cohort differed substantially by a higher female to male ratio. The Chinese and Japanese cases as east Asian groups had a lower incidence in myasthenia gravis, more wild type status in *GTF2I* and less type A or AB thymoma than their German and Indian counterparts. Nevertheless, considering the low overall number of patients and the differences in study design preclude a firm conclusion. The data, however, allow the generation of a working hypothesis.

The therapeutic options in thymomas are limited (15). While many glandular tumors are attributable to targeted therapies (16,17), to date no *GTF2I* specific drug is available. Even so, detection of this mutation may help to establish a diagnosis in small samples that are otherwise difficult to assess (7). As *GTF2I* mutated thymomas are characterized by an indolent course of disease, from the clinician's point of view the detection of this mutation is of prognostic value, but unfortunately has no therapeutic relevance so far.

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References

1. Lang M, Pausch T, Anamaterou C. Characterizing thymic tumors-how to track down rare diseases. J Thorac Dis 2022;14:4571-3.
2. Lang M, Pausch TM, Anamaterou C. Thymic neuroendocrine neoplasms-what we know, what we don't know, and what to do about it. Transl Cancer Res 2023;12:1-3.
3. Shimada M, Taniguchi H, Yamaguchi H, et al. Genetic profile of thymic epithelial tumors in the Japanese population: an exploratory study examining potential therapeutic targets. Transl Lung Cancer Res 2023;12:707-18.
4. 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.
5. Kostic Peric J, Cirkovic A, Srzentic Drazilov S, et al. Molecular profiling of rare thymoma using next-generation sequencing: meta-analysis. Radiol Oncol 2023;57:12-9.
6. Jain D, Guleria P, Singh V, et al. GTF2I Mutation in Thymomas: Independence From Racial-Ethnic Backgrounds. An Indian/German Comparative Study. Pathol Oncol Res 2021;27:1609858.
7. Oberndorfer F, Müllauer L. Genomic alterations in thymoma-molecular pathogenesis? J Thorac Dis 2020;12:7536-44.
8. Grajkowska W, Matyja E, Kunicki J, et al. AB thymoma with atypical type A component with delayed multiple lung and brain metastases. J Thorac Dis 2017;9:E808-14.
9. Radovich M, Pickering CR, Felau I, et al. The Integrated Genomic Landscape of Thymic Epithelial Tumors. Cancer Cell 2018;33:244-258.e10.
10. Lang M, Haag P, Schmidt-Gayk H, et al. Influence of ambient storage conditions and of diet on the measurement of biochemical markers of bone turnover. Calcif Tissue Int 1995;56:497.
11. Morales J, Pujar S, Loveland JE, et al. A joint NCBI and EMBL-EBI transcript set for clinical genomics and research. Nature 2022;604:310-5.
12. Feng Y, Lei Y, Wu X, et al. GTF2I mutation frequently occurs in more indolent thymic epithelial tumors and predicts better prognosis. Lung Cancer 2017;110:48-52.
13. Somerville MJ, Mervis CB, Young EJ, et al. Severe expressive-language delay related to duplication of the Williams-Beuren locus. N Engl J Med 2005;353:1694-701.
14. Van der Aa N, Rooms L, Vandeweyer G, et al. Fourteen new cases contribute to the characterization of the 7q11.23 microduplication syndrome. Eur J Med Genet 2009;52:94-100.
15. Dapergola A, Gomatou G, Trontzas I, et al. Emerging therapies in thymic epithelial tumors (Review). Oncol Lett 2023;25:84.
16. Lang M, Longerich T, Anamaterou C. Targeted therapy with vemurafenib in BRAF(V600E)-mutated anaplastic thyroid cancer. Thyroid Res 2023;16:5.
17. Lang M, Hackert T, Anamaterou C. Long-term effect of everolimus in recurrent thymic neuroendocrine neoplasia. Clin Endocrinol (Oxf) 2021;95:744-51.

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