

Stratification of follicular thyroid tumors using data-independent acquisition proteomics and a comprehensive thyroid tissue spectral library
通过数据非依赖蛋白质组学采集技术与甲状腺特异多肽谱图库对甲状腺滤泡型肿瘤的分类研究

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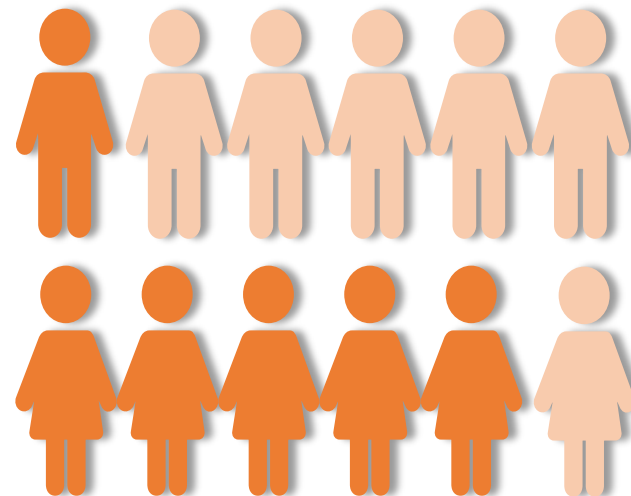
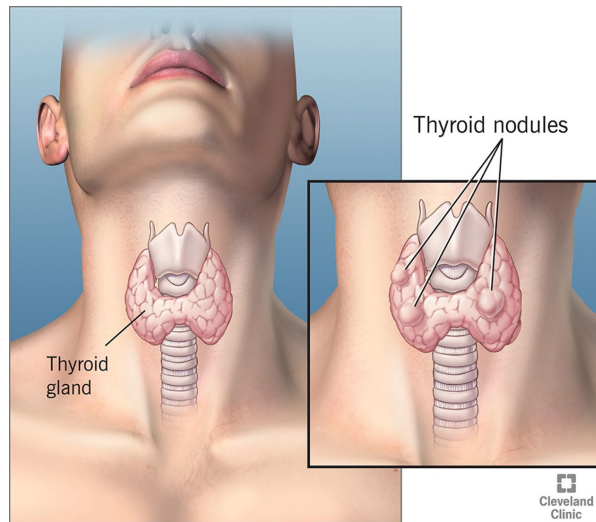
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Background of thyroid nodules

In epidemiological surveys, about **4%-7%** of the population have **palpable thyroid nodules**, compared with **17%-46% on ultrasound**, and nearly **60%** of the population have thyroid nodules reported in autopsy reports.

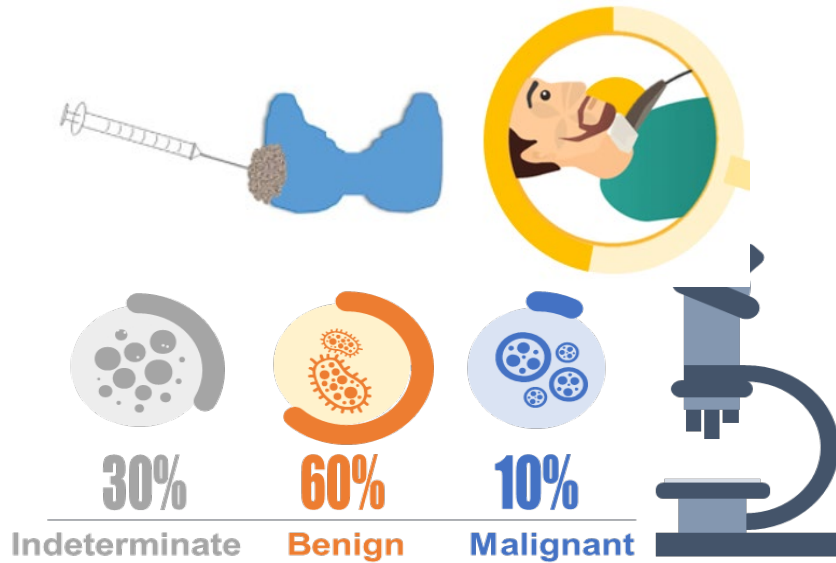
According to a statistical data on the population undergoing physical examination published in 2021, the total prevalence of thyroid nodules in **China** is about **37%** of the population.

Despite of high incidence of thyroid nodules, **only 7-15%** of them are **malignant**.

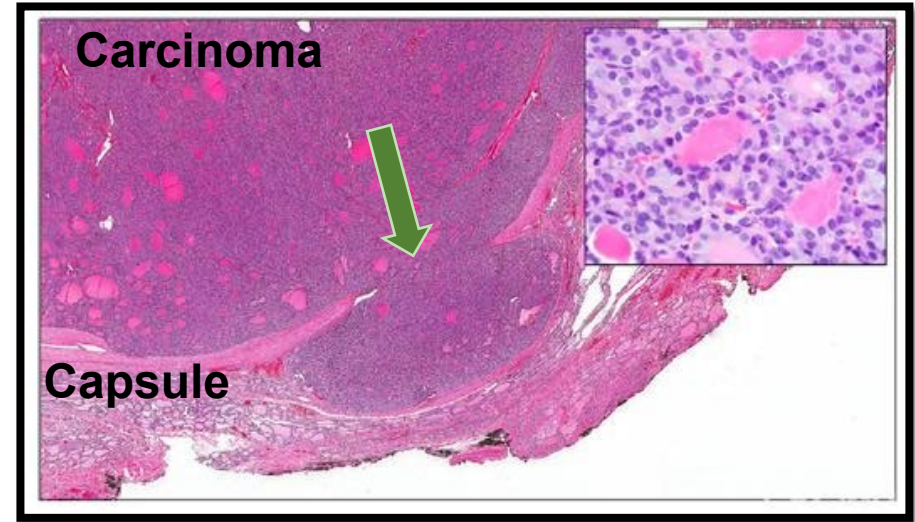


- [1] Fagin JA & Wells SA, Jr. (2016). N Engl J Med 375, 1054-1067
- [2] Li Y, et al. (2021). Front Endocrinol (Lausanne) 12, 676144
- [3] Zhou J, et al. (2020) Endocrine 70, 256-279
- [4] K. D. Burman, L. Wartofsky. (2015). N Engl J Med 373, 2347-2356
- [5] C. Durante et al. (2018). JAMA 319, 914-924

Follicular thyroid tumors



Up to 30% thyroid nodules are indeterminate before surgery.

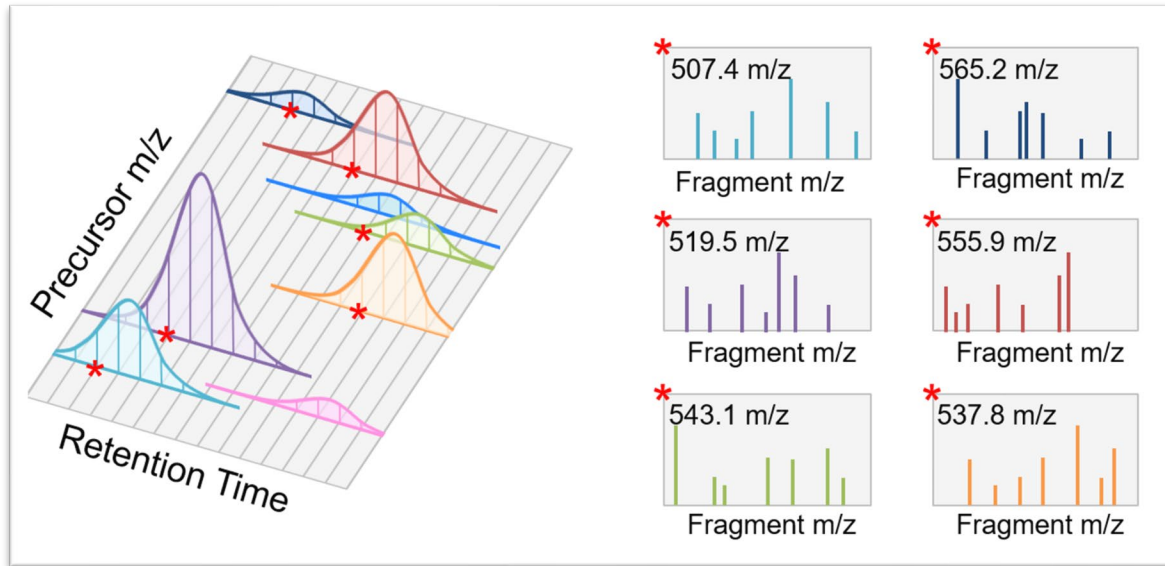


Follicular thyroid tumors cannot be distinguished before surgery.

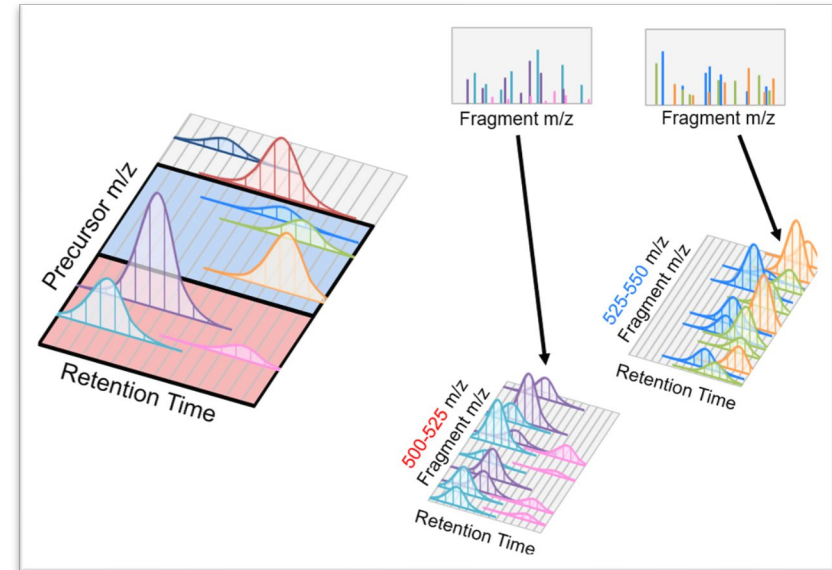
Histological difference: blood vessel and capsular invasion

Data-independent acquisition (DIA)

- DDA



- DIA

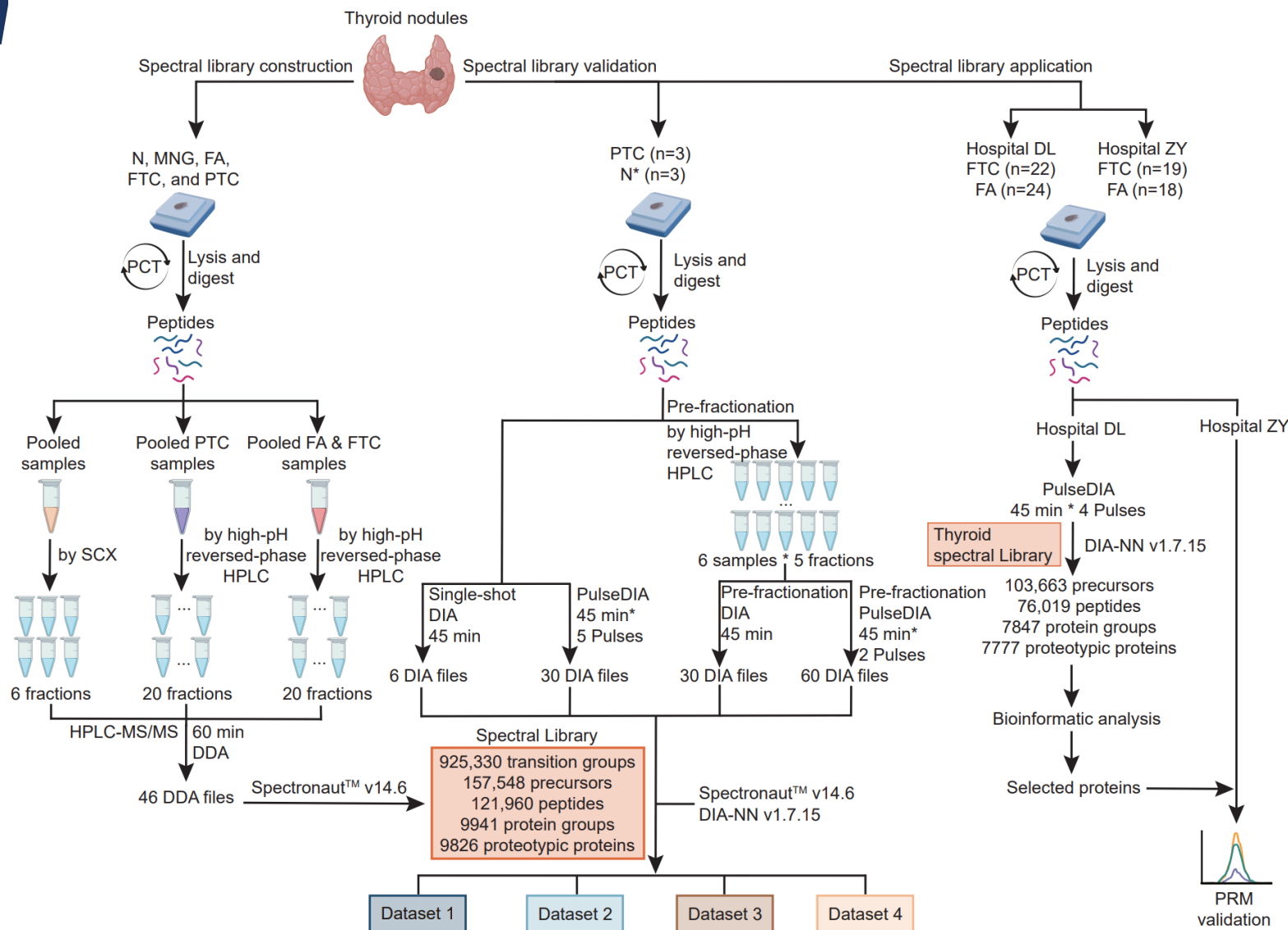


[1] Searle et al. 2020; Emma Leith, et al, 2021 EncyclopeDIA (Galaxy Training Materials).

Objectives

- To generate a comprehensive mass spectral library for human thyroid tissues
- To get insight into biological changes on different types of thyroid tumors

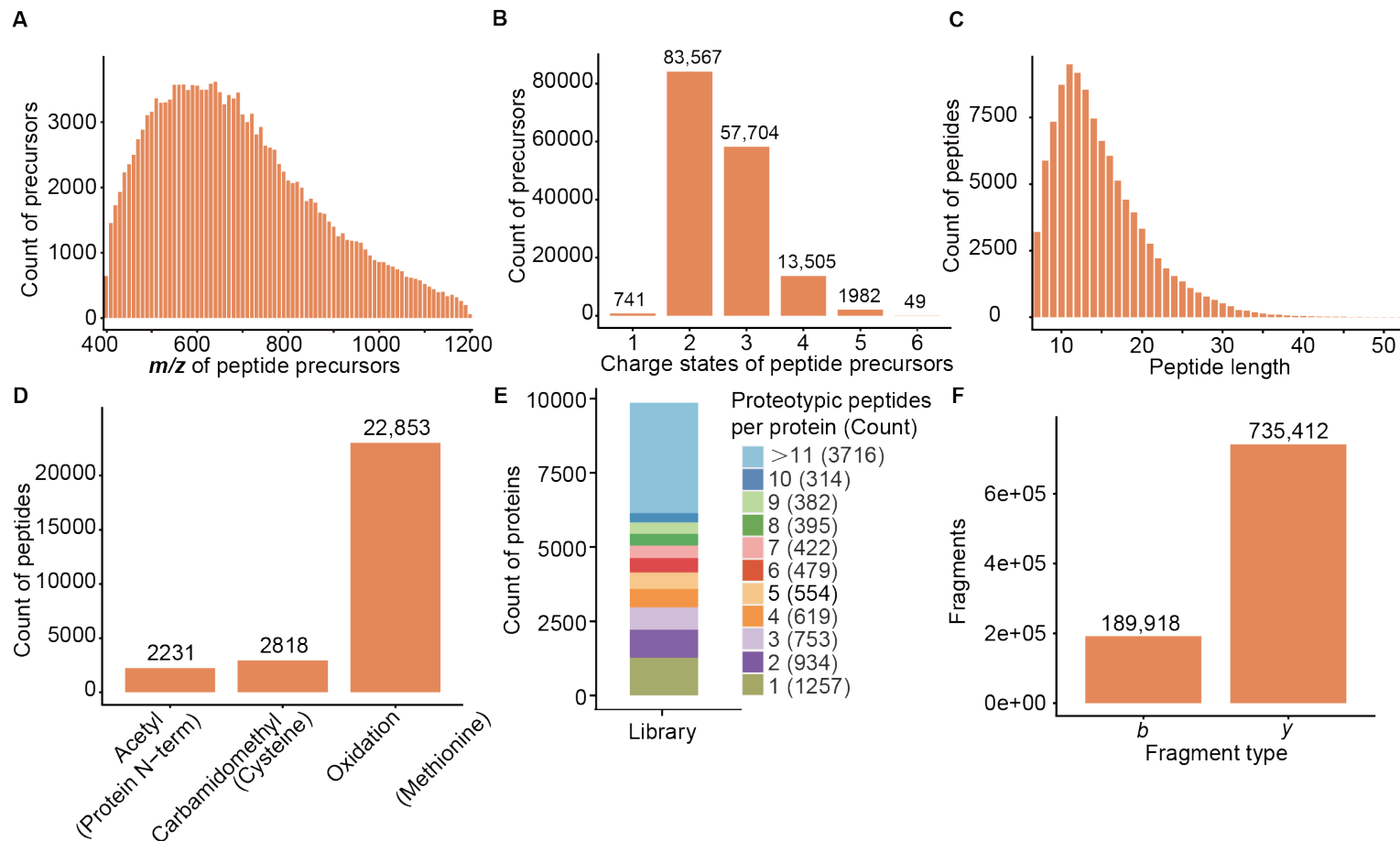
Study Design



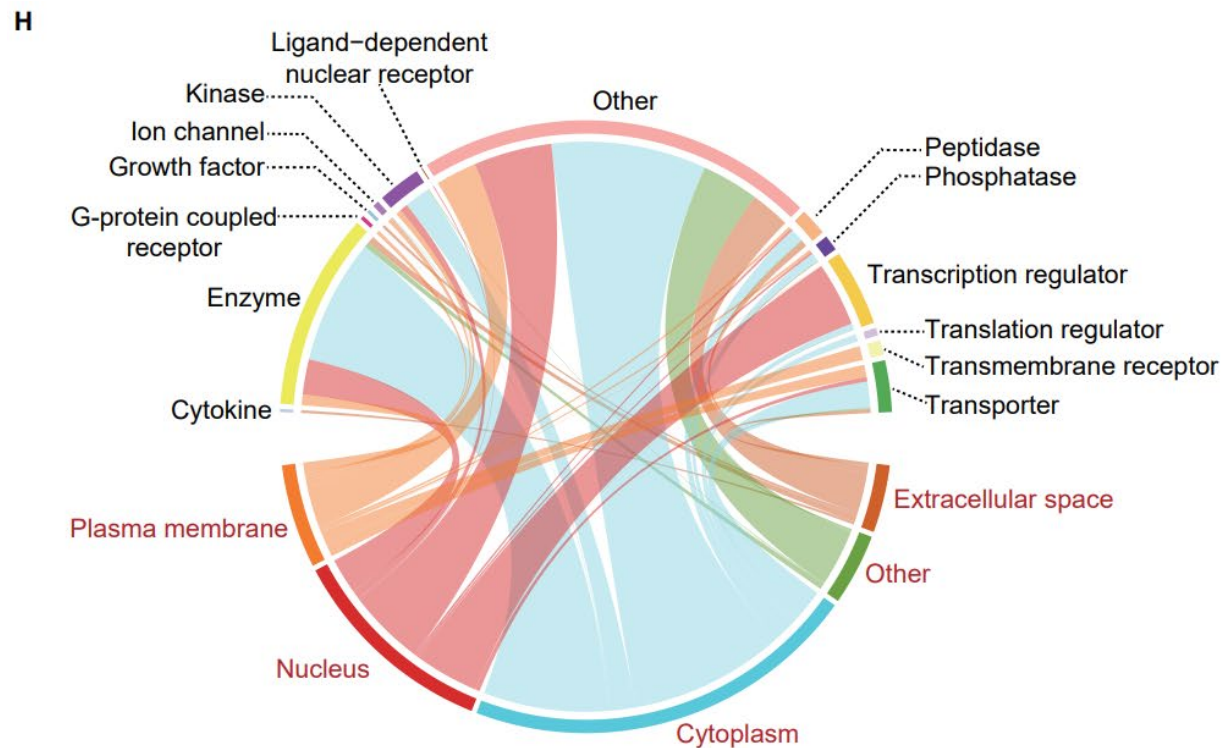
Workflow for generating a comprehensive thyroid-specific spectral library (left) and for its validation (middle) and application (right).

Characterization and statistics of the thyroid-specific spectral library

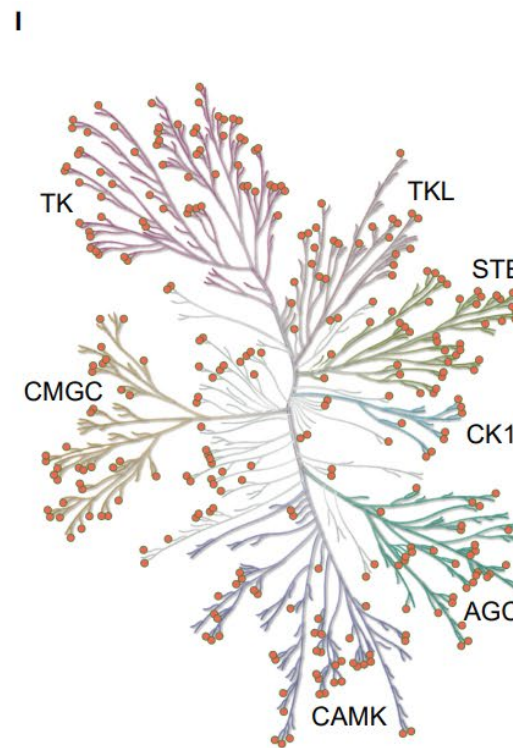
	Library
Transition groups	925,330
Peptide precursors	157,548
Peptides	121,960
Protein groups	9941
Proteotypic proteins	9826



Characterization of the thyroid-specific spectral library

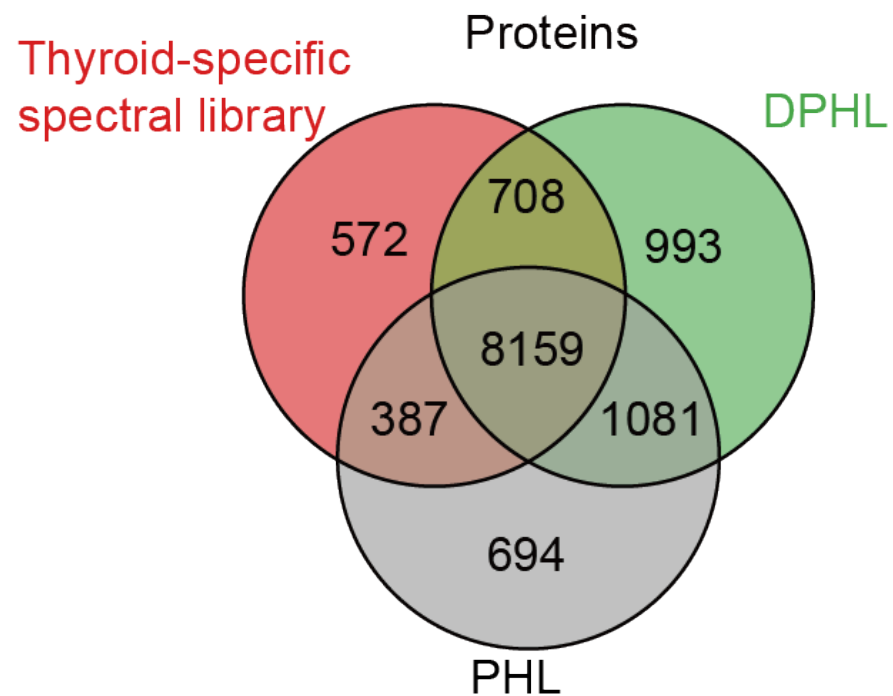
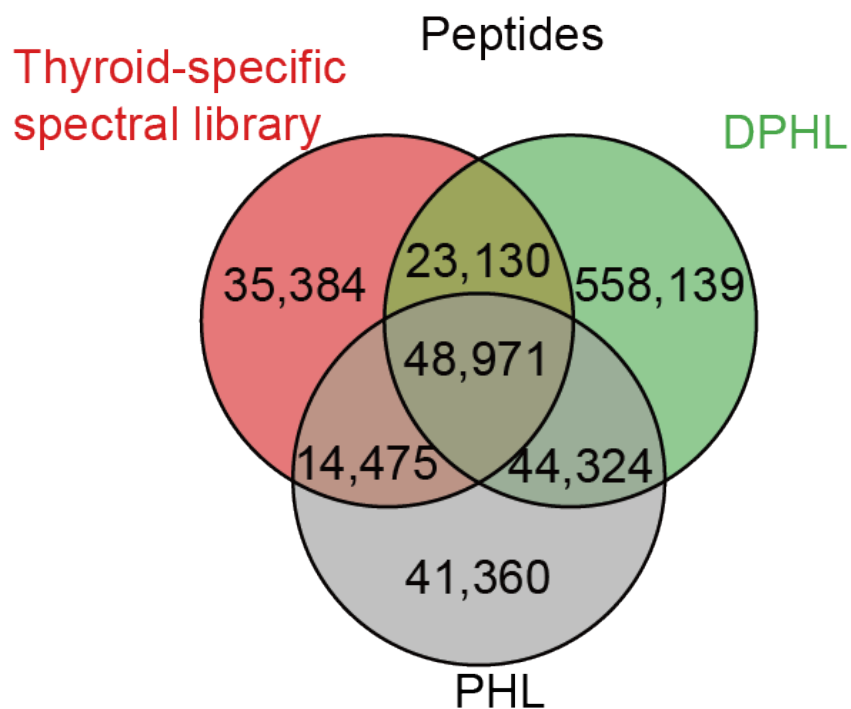


(H) Proteins are annotated according to two classification systems, subcellular location (words in red) and function type (words in black). Each curve represents one protein, linking the protein function type with the corresponding subcellular location.



(I) A total of 340 kinases (orange dots) belonging to seven families (highlighted by the different tree colors) are identified in our library.

Peptides and proteins identification comparison

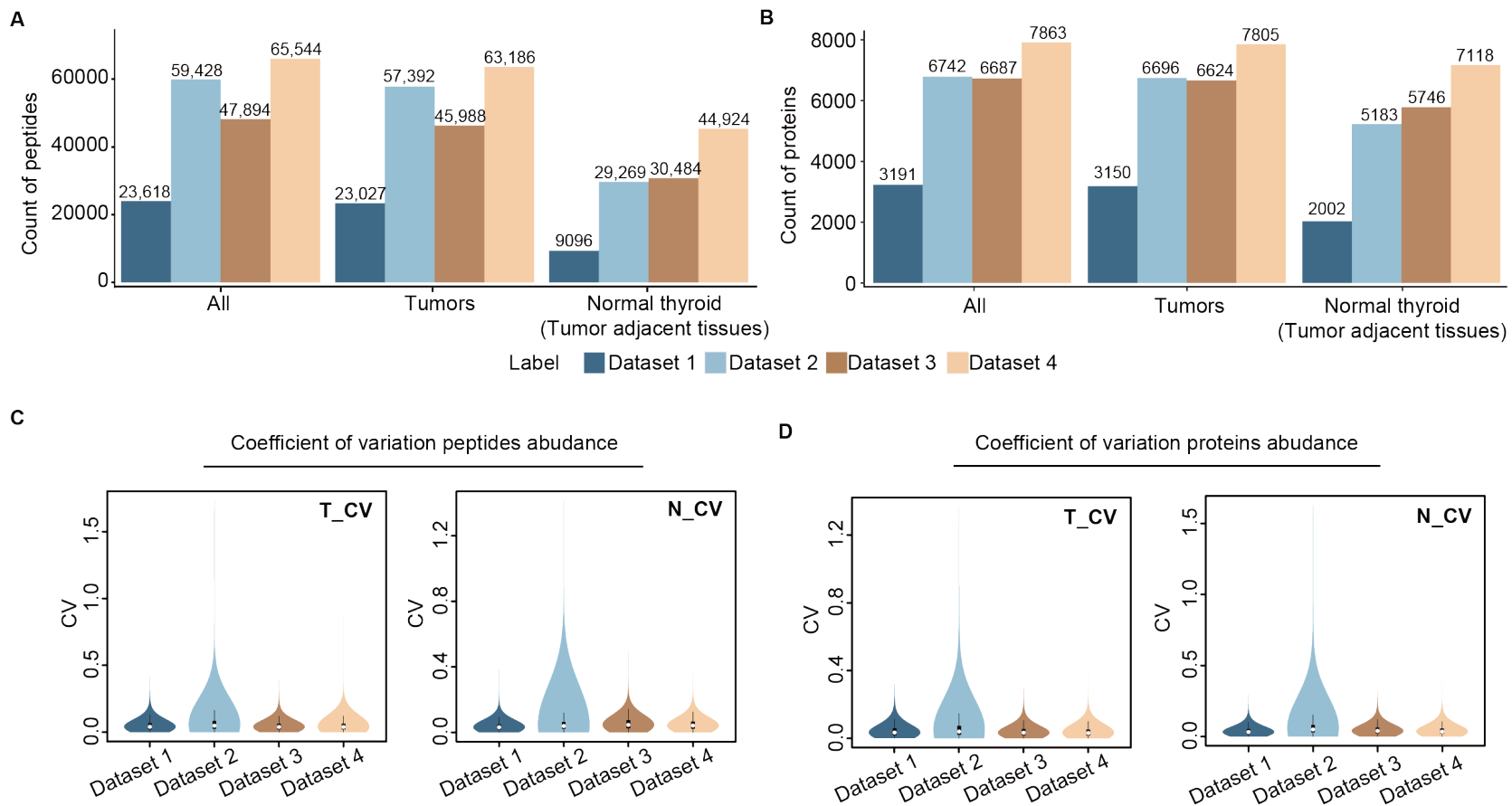


Venn diagrams of proteins and peptides in our thyroid-specific spectral library, the pan-human spectral library (PHL) and DIA pan-human spectral library (DPHL).

[1]PHL: Rosenberger G, et al (2014). Sci Data 1, 140031

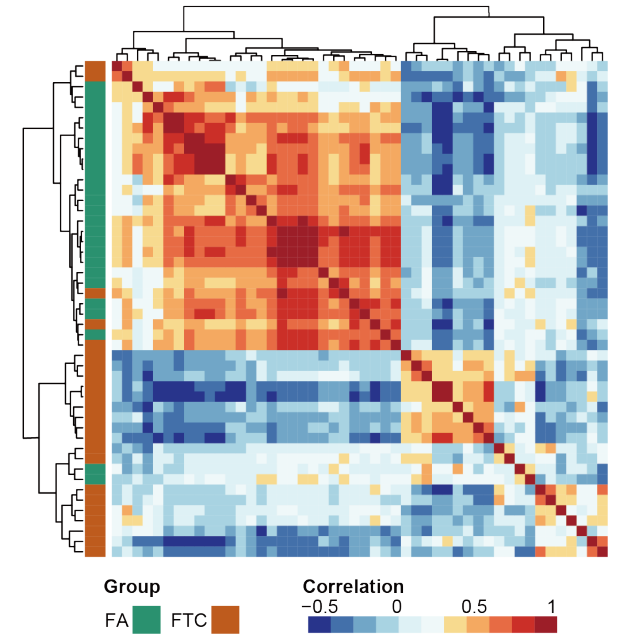
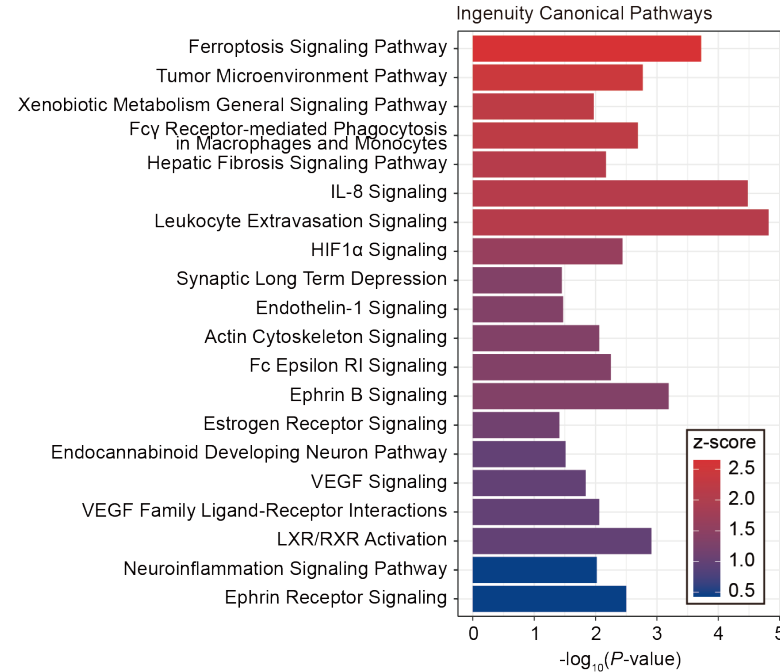
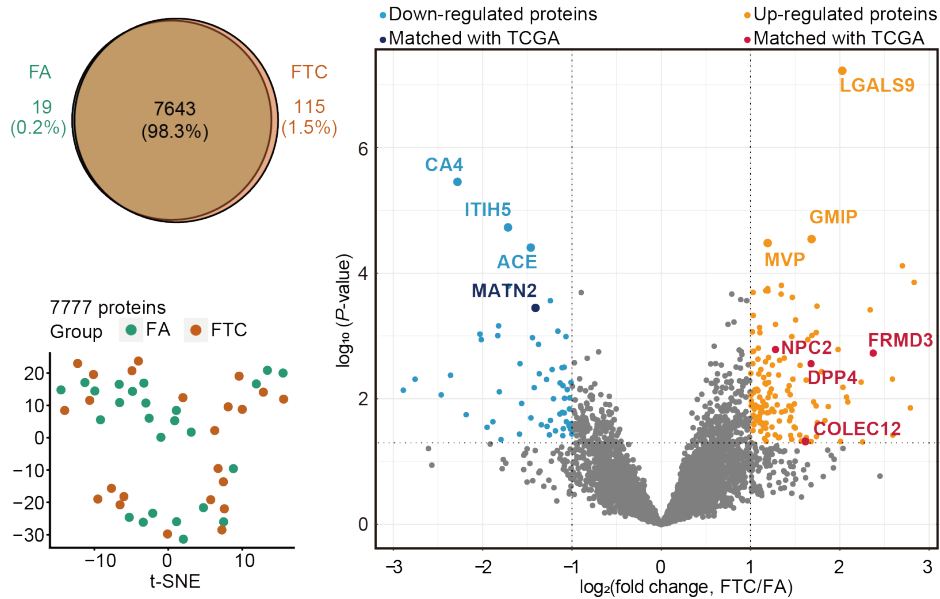
[2] DPHL: Zhu T, et al. (2020). Genomics Proteomics Bioinformatics 18, 104-119

Technical validation of the thyroid-specific spectral library



Four datasets were acquired with single-shot DIA (dataset 1), PulseDIA (dataset 2), pre-fraction DIA (dataset 3), and a combination of pre-fraction and PulseDIA (dataset 4). Identified peptides (A) and proteins (B) were obtained by searching against our thyroid-specific spectral library.

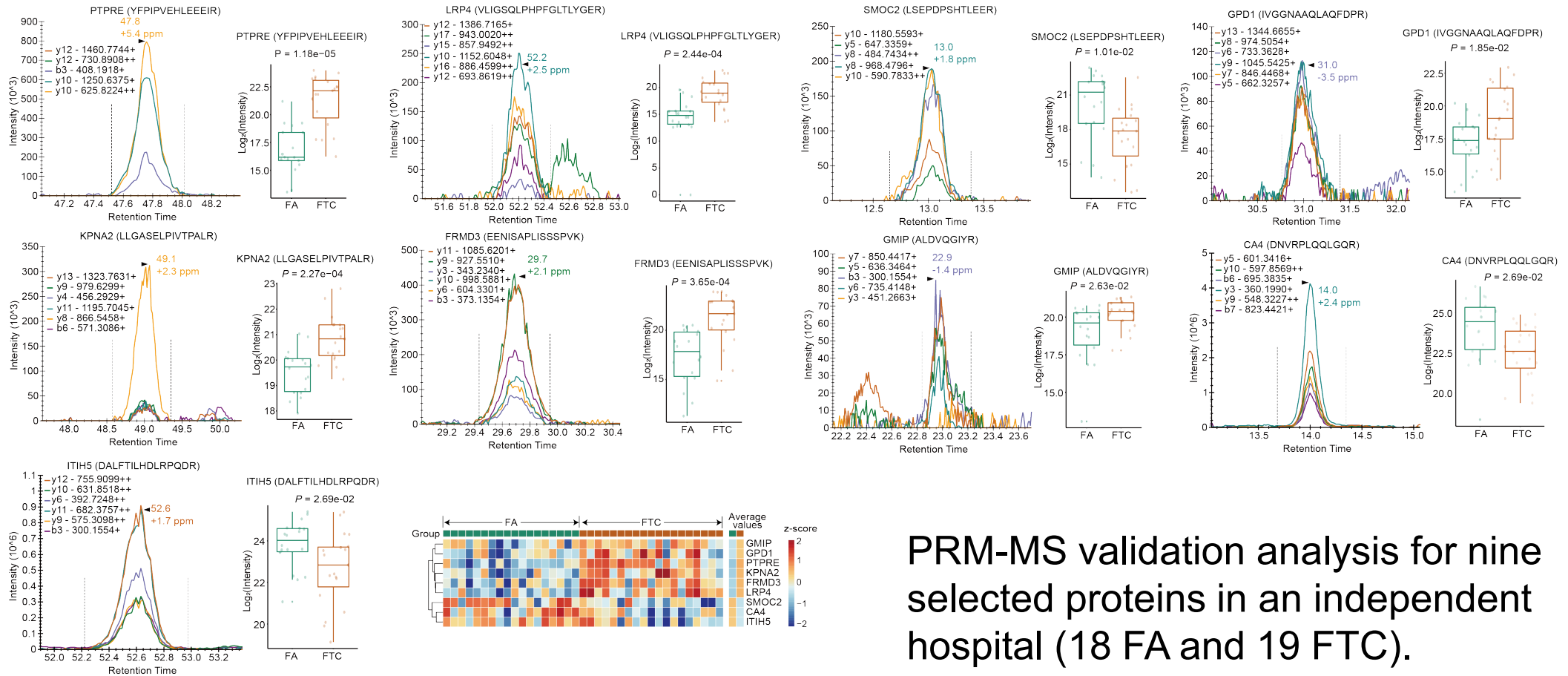
Stratification of follicular thyroid carcinoma and adenoma on proteotype



7777 proteins were identified in FA (n=24) and FTC (n=22). There were 204 DEPs comprising of 139 upregulated proteins, 56 downregulated proteins

The most activated pathway is the ferroptosis signaling pathway, which has not been demonstrated in FTC, while many more studies in other types of cancers.

Potential biomarker validated by targeted proteomics (PRM)



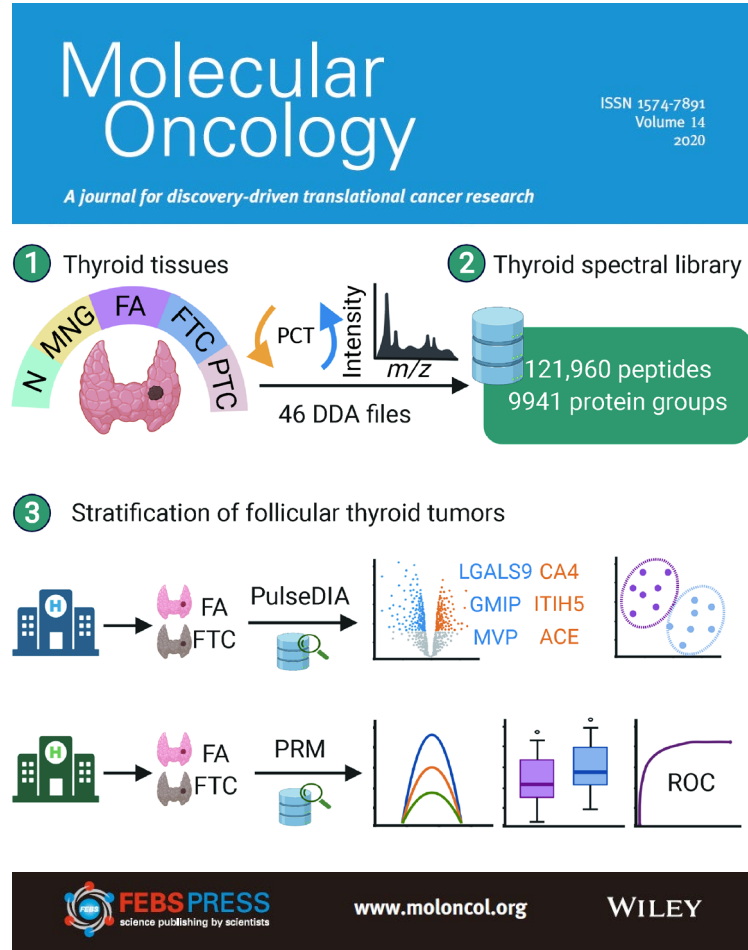
PRM-MS validation analysis for nine selected proteins in an independent hospital (18 FA and 19 FTC).

Take-home messages

Our library includes 925,330 transition groups, 157,548 peptide precursors, 121,960 peptides, 9941 protein groups, and 9826 proteins from proteotypic peptides.

Targeted assays using parallel reaction monitoring (PRM) and selected/multiple reaction monitoring S/MRM could also be developed based on this DIA library. Our established DIA library offers a valuable resource for proteomic analysis of thyroid tissue specimens.

Targeted proteomics analysis of thyroid tissue specimens and identified nine proteins can potentially distinguish FA and FTC.



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Yaoting Sun^{1,2,3,4,5*}, Lu Li^{1,2,3,4,5}, Yan Zhou^{1,2,3,4,5}, Weigang Ge⁶, He Wang^{2,3,4,5}, Runxin Wu^{2,3,4,5,7}, Wei Liu⁶, Hao Chen⁶, Qi Xiao^{1,2,3,4,5}, Xue Cai^{1,2,3,4,5}, Zhen Dong^{2,3,4,5}, Fangfei Zhang^{2,3,4,5}, Junhong Xiao⁸, Guangzhi Wang⁸, Yi He⁹, Jinlong Gao^{2,3,4,7}, Oi Lian Kon¹⁰, N. Gopalakrishna Iyer^{10,11}, Haixia Guan¹², Xiaodong Teng¹³, Yi Zhu^{2,3,4,5*}, Yongfu Zhao^{8,*}, Tiannan Guo^{1,2,3,4,5*}

Sun Y, ..., Guo T (2022). Mol Oncol, doi: 10.1002/1878-0261.13198.

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THANK YOU

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