

differentiated synovial sarcoma case underscored the limitations of this technique in detecting complex genomic rearrangements, such as the rare insertion event identified through RNA NGS and WGS. The presence of microhomology sequences at the breakpoints suggests a potential role of homologous recombination in the formation of this unique rearrangement, further complicating detection by conventional means. The integration of advanced molecular techniques, including RNA NGS and WGS, is crucial for accurate diagnosis and comprehensive understanding of the underlying genetic alterations in synovial sarcoma. These technologies not only provide a more detailed genomic landscape but also help in identifying novel and complex rearrangements that may be missed by standard assays. Future studies should focus on exploring the prevalence of such insertion-based rearrangements in FISH-negative cases and on refining diagnostic approaches to account for these complexities. This case emphasises the importance of a multimodal diagnostic strategy—combining histopathological, immunohistochemical and advanced molecular analyses—to ensure accurate diagnosis and optimal management of disease.

Data availability statement

The data and materials from this case are available from the authors on reasonable request.

Consent for publication

Informed consent for publication was obtained from the patient's parents/guardians.

Standard of reporting

The CARE guidelines (for CAse REports) were followed.

Author contributions

SX, RM: conceptualisation. RM: funding acquisition. CZ, SC: data curation. CZ: validation. DL: writing—(original draft). All authors: writing—(review and editing).

Conflicts of interest and sources of funding

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References

1. Rekhi B, Basak R, Desai SB, Jambhekar NA. Immunohistochemical validation of TLE1, a novel marker, for synovial sarcomas. *Indian J Med Res* 2012;136:766–75.
2. Ladanyi M, Antonescu CR, Leung DH, et al. Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: a multi-institutional retrospective study of 243 patients. *Cancer Res* 2002;62:135–40.
3. Yoshida A, Arai Y, Satomi K, et al. Identification of novel SSX1 fusions in synovial sarcoma. *Mod Pathol* 2022;35:228–39.
4. Kadoch C, Crabtree GR. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell* 2013;153:71–85.
5. Baranov E, McBride MJ, Bellizzi AM, et al. A novel SS18-SSX fusion-specific antibody for the diagnosis of synovial sarcoma. *Am J Surg Pathol* 2020;44:922–33.
6. Ten Heuvel SE, Hoekstra HJ, Suurmeijer AJ. Diagnostic accuracy of FISH and RT-PCR in 50 routinely processed synovial sarcomas. *Appl Immunohistochem Mol Morphol* 2008;16:246–50.
7. Köse D, Annagür A, Erol C, et al. Synovial sarcoma in a premature newborn. *Pediatr Int* 2014;56:e17–20.
8. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879–86.
9. Gounder M, Schöffski P, Jones RL, et al. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. *Lancet Oncol* 2020;21:1423–32.
10. Kadoch C, Hargreaves DC, Hodges C, et al. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet* 2013;45:592–601.
11. Stacchiotti S, Van Tine BA. Synovial sarcoma: current concepts and future perspectives. *J Clin Oncol* 2018;36:180–7.
12. de Bruijn DR, Geurts van Kessel A. Common origin of the human synovial sarcoma associated SS18 and SS18L1 gene loci. *Cytogenet Genome Res* 2006;112:222–6.
13. Storlazzi CT, Mertens F, Mandahl N, et al. A novel fusion gene, SS18L1/SSX1, in synovial sarcoma. *Genes Chromosomes Cancer* 2003;37:195–200.
14. Ottaviani D, LeCain M, Sheer D. The role of microhomology in genomic structural variation. *Trends Genet* 2014;30:85–94.
15. Hatch EM, Fischer AH, Deerink TJ, Hetzer MW. Catastrophic nuclear envelope collapse in cancer cell micronuclei. *Cell* 2013;154:47–60.

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Mutation-tissue specificity in *DICER1* syndrome: insights from familial pleuropulmonary blastoma and a pan-tumour hotspot analysis



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To the Editor,

DICER1 syndrome is an autosomal-dominant tumour predisposition disorder caused by germline mutations in the *DICER1* gene, which

confers an increased risk for a spectrum of neoplasms including pleuropulmonary blastoma (PPB). Type I PPB, characterised by cystic lung lesions, may be clinically or radiologically misinterpreted as congenital pulmonary airway malformation (CPAM) due to overlapping clinical and radiological features.

We report two sisters who presented with cystic lung lesions initially diagnosed as CPAM, but were subsequently confirmed as having type I PPB based on molecular testing. Family screening revealed that the mother carried the identical *DICER1* germline mutation and had thyroid nodules, whereas another sister was an asymptomatic carrier. Both affected siblings harboured a second-hit mutation in their lung tumours

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targeting the *DICER1* residue Glu1813. Given the established role of second-hit mutations of *DICER1* as change-of-function events, we investigated whether specific *DICER1* hotspot mutations may show tumour-type preference. A systematic analysis of 398 second-hit mutations across 14 tumour tissue categories from a public database demonstrated a highly significant association between mutation type and tumour tissue of origin [$\chi^2(52)=232.8$, $p<0.0001$]. This study highlights the diagnostic challenges in distinguishing PPB from CPAM, emphasises the importance of *DICER1* molecular testing in familial settings, and suggests that mutation-specific oncogenic mechanisms may influence histologic phenotype.

DICER1 is a crucial RNase III enzyme responsible for processing precursor microRNAs (miRNAs) into mature miRNAs, which regulate gene expression by targeting mRNAs for degradation or translational repression.^{1,2} Germline *DICER1* mutations cause *DICER1* syndrome, an autosomal-dominant disorder with an increasing risk of various neoplasms, including PPB, ovarian Sertoli–Leydig cell tumour (SLCT), cystic nephroma, thyroid nodules, and differentiated thyroid carcinoma.³ PPB, a rare and aggressive paediatric lung malignancy, is the most common primary lung tumour in children.⁴

PPB is classified into three histological subtypes: type I (purely cystic), type II (cystic and solid), and type III (entirely solid).⁵ Type I PPB, the least aggressive tumour, may be clinically or radiologically misinterpreted as a CPAM, a benign lung lesion, due to overlapping features.⁵ Although histological distinction is usually possible, some cases may pose diagnostic challenges. Unlike CPAM, type I PPB can progress to more severe stages, emphasising the need for accurate diagnosis. Molecular detection of *DICER1* mutations is the key to differential diagnosis. Approximately 90% of PPBs are associated with germline mutations in the *DICER1* gene, which follows the ‘two-hit’ model, with a germline loss-of-function mutation (first hit) paired with a somatic missense mutation often in the RNase IIIb domain (second hit).⁵

The prevalence of *DICER1* syndrome is not fully established, but it is often underdiagnosed due to variable penetrance and a broad range of associated tumours.^{2,6–8} This report details two sisters with type I PPB and their genomic alterations, initially misdiagnosed as CPAM, highlighting the essential role of molecular diagnostics in accurate diagnosis and management and the need for increased clinician awareness.

Patient 1: A 2-year-10-month-old girl presented with a persistent cough and recurrent respiratory distress. Chest computed tomography (CT) revealed a large, septated, air-filled lesion in the right hemithorax compressing adjacent lung tissue and a smaller 2.5-cm cystic lesion in the left upper lobe (Fig. 1A). A thoracoscopic resection of the right lung bulla was performed first, followed by a wedge resection of the left upper lobe. The wedge resection specimen, measuring 3.5×0.5×0.5 cm, was received for histopathologic evaluation. Grossly, the specimen appeared greyish brown, with a solid, spongy, and soft cut surface. The initial microscopic examination revealed features consistent with CPAM. However, an extensive review of additional tissue blocks identified a small nodule of immature cartilage within the septa, a finding seen in approximately 40% of type I PPBs and highly characteristic of the diagnosis (Fig. 1B–C).

Patient 2: A 10-month-old girl, the younger sister of patient 1, presented with respiratory distress and cough shortly after birth. Chest CT at 10 months revealed a large, air-filled, septated cystic lesion in the right hemithorax, causing significant compression and displacement of the right lung parenchyma (Fig. 1D). The cystic lesion was resected thoracoscopically. A cyst-like specimen measuring 7.0×4.0×0.6 cm was submitted for histopathologic evaluation. The initial microscopic examination revealed a cystic structure, prompting consideration of a benign malformation. However, a subsequent thorough review found an area of rhabdomyoblasts, a hallmark of PPB (Fig. 1).

Targeted next-generation sequencing (NGS) of 638 cancer-related genes was performed on both surgical and peripheral blood specimens from each sibling. The analysis showed a shared germline *DICER1* frameshift mutation, *DICER1* c.5315_5316del p.F1772Cfs*6, detected in both tumour tissues and peripheral blood samples. Additionally, both siblings harboured distinct somatic *DICER1* mutations in their tumour specimens: Patient 1 had *DICER1* c.5437G>A p.E1813K [variant allele frequency (VAF) 10.2%], and patient 2 had *DICER1* c.5438A>G p.E1813G (VAF 14.8%). These somatic mutations, occurring in trans to the germline mutation, support the two-hit model of tumour suppressor gene inactivation.

Patient 1 also exhibited three additional somatic mutations of uncertain significance: *BARD1* c.1109G>A, p.R370H (VAF 5.7%), *FAT1* c.632A>C, p.D211A (VAF 8.2%), and *GID4* c.1A>G, p.M1? (VAF

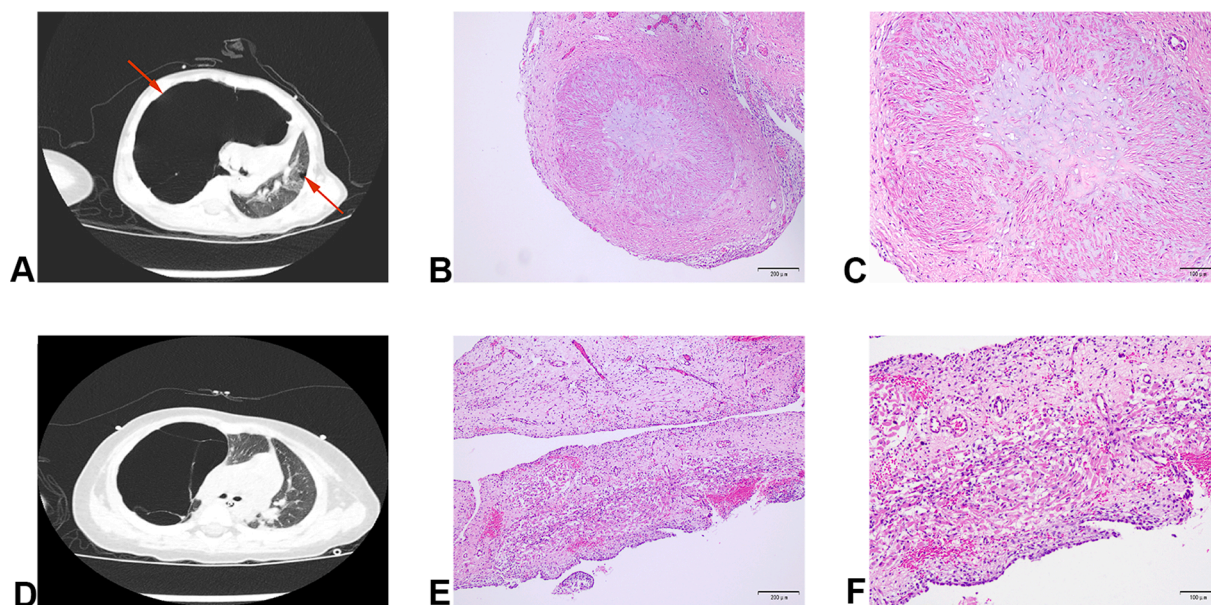


Fig. 1. Chest CT findings of patient 1 and patient 2. (A) Axial chest CT of patient 1 shows a large cystic lesion in the right hemithorax and a smaller lesion in the left upper lobe (red arrows). (B, C) Histopathology from patient 1 (H&E stain) showed a nodule of immature cartilage within the septal wall. (D) Axial chest CT of patient 2 reveals a large, septated cystic lesion compressing the right lung. (E, F) H&E stain from patient 2 showed an area of rhabdomyoblasts, a hallmark feature of PPB. CT, computed tomography; H&E, haematoxylin and eosin; PPB, pleuropulmonary blastoma.

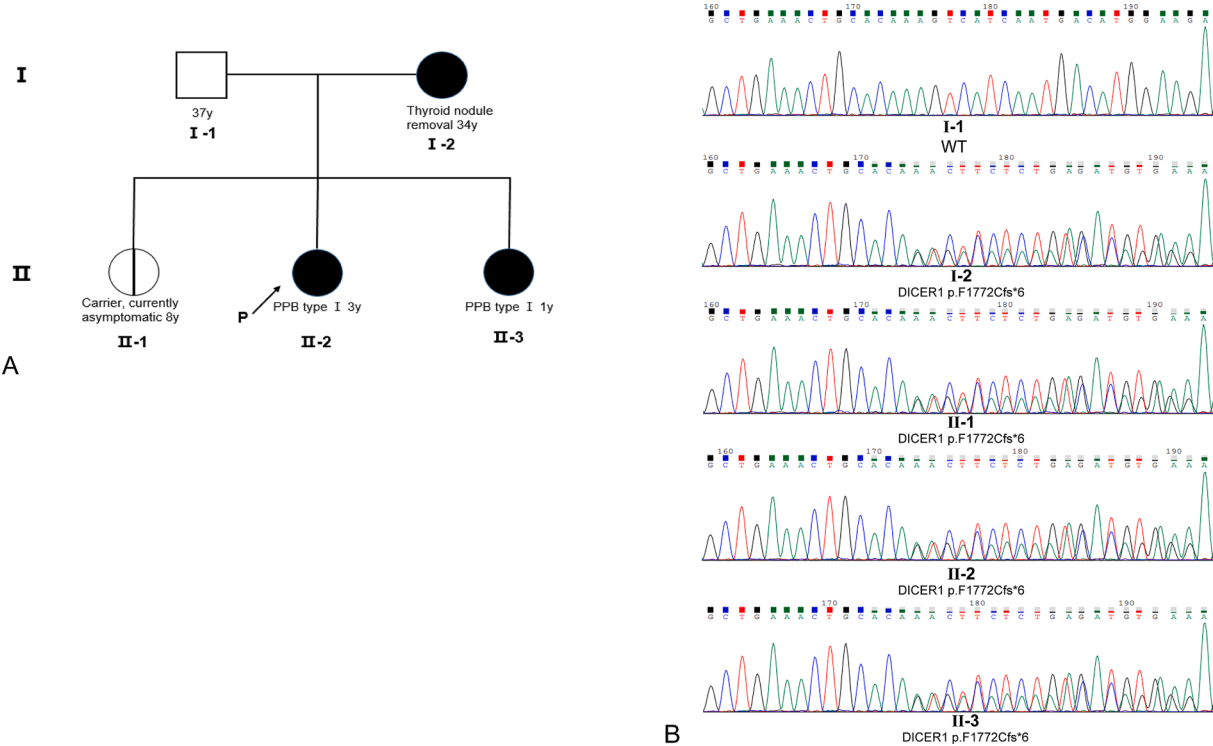


Fig. 2. Transmission of the *DICER1* germline mutation in the family. (A) Family pedigree showing that the mother and all three daughters carry the *DICER1* germline mutation. The mother had thyroid nodules, two daughters had PPB, and one daughter remains disease-free at age 8. (B) PCR and Sanger sequencing results for all family members. Arrowheads indicate the location of the *DICER1* c.5315_5316del (p.F1772Cfs*6) mutation. PCR, polymerase chain reaction; PPB, pleuropulmonary blastoma.

12.9%). No additional somatic mutations were identified in patient 2. Both tumours showed no gross chromosomal structural or numerical abnormalities.

Family members were tested for the germline *DICER1* mutation using polymerase chain reaction (PCR) amplification with gene-specific primers (F_*DICER1* e25: CAGTTCACCTCGTGCTCCCA; R_*DICER1* e25: ATGCTTCTGCACAAGCTTACG). Both the mother and the elder sister were found to carry the same *DICER1* frameshift mutation, c.5315_5316del, p.Phe1772Cysfs*6. The mother had previously

undergone surgical removal of thyroid nodules, while the elder sister, now 8 years old, remains asymptomatic (Fig. 2).

Both siblings had somatic second-hit mutations in their lung tumours affecting the same *DICER1* residue, p.E1813. Given the established role of such mutations as change-of-function events and the tissue-specific nature of miRNA expression, we investigated whether particular *DICER1* hotspot mutations are associated with tumour-type specificity.

In *DICER1* syndrome, somatic mutations cluster at five hotspot residues within the RNase IIIb domain: p.E1705, p.D1709, p.G1809, p.D1810, and

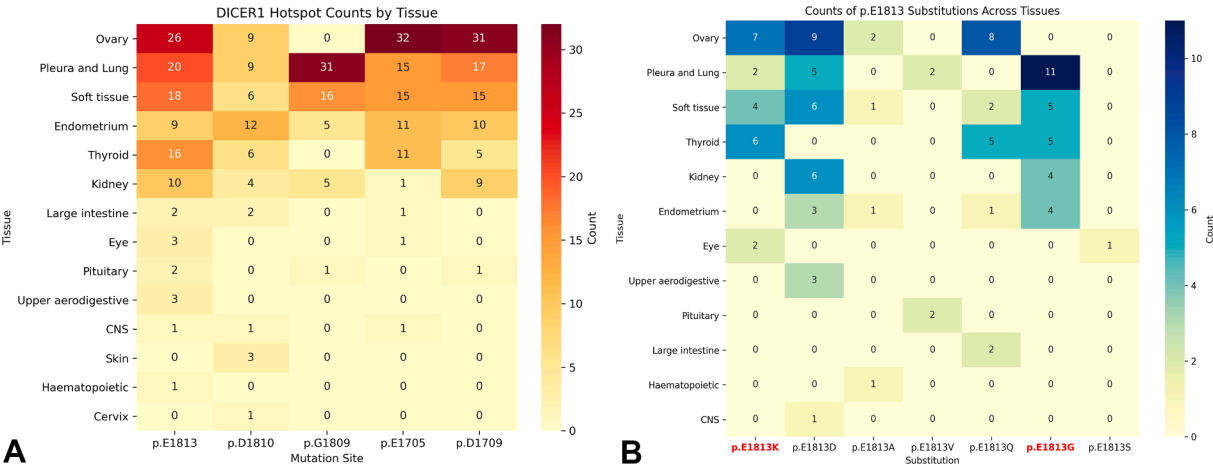


Fig. 3. Distribution of *DICER1* somatic mutations across tumour types compiled from the Catalogue Of Somatic Mutations In Cancer (COSMIC) database. (A) Heatmap of *DICER1* somatic hotspot mutations across 14 tumour categories. (B) Heatmap of specific amino acid substitutions at the p.E1813 hotspot across 12 tumour categories. In both panels, each cell displays the absolute count, with the standardised residual from the chi-square analysis shown in parentheses. A positive residual indicates enrichment (observed count > expected count), while a negative residual indicates depletion. Residuals corresponding to statistical significance after Bonferroni correction are highlighted: red indicates significant enrichment, and blue indicates significant depletion. The significance thresholds were set at $|\text{residual}| > 3.38$ for panel A and $|\text{residual}| > 3.36$ for panel B.

p.E1813. To explore whether specific residue mutations are associated with particular tumour types, we analysed 398 somatic *DICER1* mutations from the Catalogue Of Somatic Mutations In Cancer (COSMIC) database across 14 tumour categories. A chi-square test of independence (14 tissues $\times$ 5 mutation sites) revealed a highly significant association between mutation sites and tissue of origin [$\chi^2(52)=232.8, p<0.0001$]. To identify specific mutation-tissue associations, we examined standardised residuals using a Bonferroni-corrected significance threshold for multiple comparisons (70 comparisons; adjusted $\alpha=0.000714$; critical |residual| ≈ 3.38). This analysis showed that the p.G1809 mutation was significantly enriched in pleural and lung tumours (primarily PPB) (observed=31, expected=13.4, residual=4.78) and notably absent in ovarian tumours (mostly SLCT) (observed=0, expected=14.3, residual=-3.79). Although p.G1809 represents the most frequent RNase IIIb hotspot in pleuropulmonary tumours according to COSMIC (42% of lung/pleura cases), several studies have reported different second-hit mutations, including p.E1813K, p.E1813G, p.D1810, and p.G1809 within the same histological context.^{5,7}

Consistent with this heterogeneity, the two sisters described here both carried p.E1813 substitutions (p.E1813K and p.E1813G), underscoring that multiple hotspot variants can drive type I PPB and that the exact residue change may be secondary to the selective pressure for 5p miRNA loss in lung tissue. Other trends including an increased prevalence of p.E1705 (residual=2.22) and p.D1709 (residual=2.00) in ovarian tumours, p.E1813 (residual=1.65) in thyroid tumours, and p.G1809 in soft tissue tumours (residual=1.86) and its absence in thyroid tumours (residual=-2.35) (Fig. 3A). However, these results did not reach statistical significance under the Bonferroni correction. A larger sample size may be needed to confirm additional mutation-tissue associations.

We next investigated whether different amino acid substitutions at the same *DICER1* hotspot location are associated with specific tumour types. A total of 111 mutations of p.E1813 were compiled from 12 distinct tissue categories, including the following substitutions: p.E1813K, p.E1813D, p.E1813A, p.E1813V, p.E1813Q, and p.E1813G. A chi-square test of independence on the resulting contingency table (12 tissues $\times$ 6 substitutions) revealed a significant association between the type of E1813 substitution and tissue of origin [$\chi^2(55)=112.7, p<0.0001$], indicating that these substitutions are not randomly distributed across tumour types (Fig. 3B). To identify specific associations, we analysed the standardised residuals for each substitution-tissue pair. This analysis revealed several trends that, while informative, did not reach statistical significance after a strict Bonferroni correction. For instance, the p.E1813G was significantly under-represented in ovarian tumours (residual=-2.61) but enriched in pleural and lung tumours (residual=2.53). Similarly, the p.E1813D was enriched in the upper aerodigestive tissues (residual=2.23) but depleted in thyroid tumours (residual=-2.18). These patterns suggest that different substitutions may indeed have distinct tissue tropisms, though a larger cohort would be required to validate these associations.

A differential diagnosis between type I PPB and CPAM is challenging due to overlapping clinical, radiological, and histological features.^{9,10} While both present as cystic lung lesions, CPAM is a non-neoplastic developmental anomaly, whereas type I PPB is a neoplastic proliferation with malignant potential, necessitating early intervention.^{1,5} In our case, both siblings were initially misdiagnosed, reflecting common diagnostic pitfalls. The International Pleuropulmonary Blastoma Registry (IPPB) notes that the misdiagnosis is often due to overlooked subtle primitive mesenchymal cells in type I PPB.⁵ These diagnostic challenges underscore the critical role of *DICER1* mutation testing and support current recommendations for germline analysis in paediatric cystic lung lesions, particularly those that are bilateral, septated, or recurrent or occur in the context of a suggestive family history.^{3,11}

DICER1 syndrome exhibits significant variability in tumour risk and clinical presentation. In this family, in addition to the siblings with PPB, both the mother and the elder sister also carried the germline *DICER1* mutation. While the mother had thyroid nodules,

the elder sister remained asymptomatic. This variability in penetrance and tumour types is well documented.¹² As with other inherited cancer syndromes, lifelong surveillance is essential for all *DICER1* mutation carriers to enable early detection and management of associated neoplasms.^{3,13}

DICER1 plays a central role in miRNA biogenesis by processing precursor miRNAs (pre-miRNAs), which are short hairpin-shaped structures derived from primary transcripts. *DICER1* cleaves the terminal loop of these pre-miRNAs to generate 22-nucleotide miRNA duplexes, each composed of two strands: one from the 5' arm (5p) and one from the 3' arm (3p). Typically, one strand, designated the guide strand, is preferentially incorporated into the RNA-induced silencing complex (RISC) to mediate gene silencing, while the other strand is degraded. In cells with wild-type *DICER1*, balanced production of 5p and 3p miRNAs ensures proper regulation of both oncogenes and tumour suppressor genes. Generally, 5p miRNAs are enriched in tumour-suppressive functions, whereas 3p miRNAs have oncogenic potential. The RNase IIIa domain of *DICER1* cleaves the 3p arm, while the RNase IIIb domain processes the 5p arm. In *DICER1*-related tumours, recurrent hotspot mutations occur in the RNase IIIb domain, selectively impairing 5p miRNA processing. As a result, 5p species are depleted, 3p species accumulate disproportionately, and the skewed 3p-to-5p ratio disrupts normal gene regulatory networks.

DICER1 syndrome differs from classic inherited cancer syndromes in that the second-hit somatic mutations are not loss-of-function mutations but rather change-of-function mutations.¹⁴ These mutations cluster in the RNase IIIb domain of *DICER1*, which is specifically responsible for cleaving the 5p strand of the pre-miRNA. Therefore, these mutations selectively impair the 5p miRNAs, while 3p miRNAs remain unaffected.¹⁵ Theoretically, the location and/or type of mutations within the RNase IIIb domain could differentially impact *DICER1*'s enzymatic activity, leading to altered miRNA profiles and contributing to tissue-specific tumorigenesis. To investigate this, we analysed 398 somatic *DICER1* hotspot mutations from the COSMIC database across 14 tumour tissue categories. A chi-square test revealed a significant association between mutation location and tumour tissue of origin ($p<0.0001$). After Bonferroni correction, the p.G1809 mutation was significantly enriched in pleura and lung tumours (primarily PPB) and completely absent in ovarian tumours (primarily SLCT).

Interestingly, among the five major *DICER1* RNase IIIb hotspots, p.E1705, p.D1709, p.G1809, p.D1810, and p.E1813, four involve acidic residues essential for metal-ion coordination, which is critical for catalytic activity. In contrast, G1809 is a non-polar residue that contributes structurally rather than catalytically. This distinction suggests that the p.G1809 mutation may affect RNase IIIb function differently, possibly leading to unique patterns of tissue-specific miRNA disruption. Finally, we observed a non-random distribution of amino acid substitutions at the E1813 hotspot across tumour types. Although these patterns did not reach statistical significance after correction for multiple comparisons, likely due to limited sample size, they support the hypothesis that both the position and specific amino acid change can shape tissue-specific oncogenic processes in *DICER1* syndrome.

In conclusion, this study describes a family affected by *DICER1* syndrome that was initially misdiagnosed as CPAM, underscoring the critical role of molecular diagnostics in differential diagnosis. We also investigated *DICER1* mutation patterns and their potential association with tissue-specific tumour development. While our findings suggest a possible link, further functional studies are necessary to confirm their biological significance.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Affiliated Children's Hospital of Xiangya School of Medicine (HCHLL-2018-43). Written informed consent was obtained from the parents.

Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

WF, GY and SX conceptualised and developed the study methodology; GY acquired funding; JW and WC curated the data; SC and HC conducted validation; HR wrote the original draft; all authors contributed to writing-review and editing, and approved the final manuscript.

Conflicts of interests and sources of funding

HR, SC, HC, and SX are employees of Suzhou SANO Precision Medicine Ltd. The other authors declare that the research was conducted without any commercial or financial relationships that could be perceived as a potential conflict of interest. This study was funded by Hunan Provincial Natural Science Foundation (2020SK50504).

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References

- Gonzalez IA, Stewart DR, Schultz KAP, Field AP, Hill DA, Dehner LP. DICER1 tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma. *Mod Pathol* 2022;35:4–22.
- Robertson JC, Jorczyk CL, Oxford JT. DICER1 syndrome: *DICER1* mutations in rare cancers. *Cancers (Basel)* 2018;10:143.
- Schultz KAP, Williams GM, Kamihara J, et al. DICER1 and associated conditions: identification of at-risk individuals and recommended surveillance strategies. *Clin Cancer Res* 2018;24:2251–61.
- Abele M, Voggel S, Bremensdorfer C, et al. Incidences and characteristics of primary lung malignancies in childhood in Germany: an analysis of population-based data from German cancer registries. *Pediatr Blood Cancer* 2022;69:e29744.
- Hill DA, Jarzembowski JA, Priest JR, Williams G, Schoettler P, Dehner LP. Type I pleuropulmonary blastoma: pathology and biology study of 51 cases from the International Pleuropulmonary Blastoma Registry. *Am J Surg Pathol* 2008;32:282–95.
- Caroleo AM, De Ioris MA, Boccuto L, et al. DICER1 syndrome and cancer predisposition: from a rare pediatric tumor to lifetime risk. *Front Oncol* 2020;10:614541.
- de Kock L, Sabbaghian N, Druker H, et al. Germ-line and somatic *DICER1* mutations in pineoblastoma. *Acta Neuropathol* 2014;128:583–95.
- Novokreshennih EE, Kolodkina AA, Bezlepina OB. DICER1 syndrome: clinical variety endocrine manifestations and features of diagnostics. *Probl Endokrinol (Mosk)* 2023;70:78–85.
- Saez BJ, Pattillo SJ, Vuletin SJ. Pleuro-pulmonary blastoma presenting as a chest wall deformity: a case report. *Rev Chil Pediatr* 2018;89:231–5.
- Leblanc C, Baron M, Desselas E, et al. Congenital pulmonary airway malformations: state-of-the-art review for pediatrician's use. *Eur J Pediatr* 2017;176:1559–71.
- Knight S, Knight T, Khan A, Murphy AJ. Current management of pleuropulmonary blastoma: a surgical perspective. *Children (Basel)* 2019;6:86.
- Stewart DR, Best AF, Williams GM, et al. Neoplasm risk among individuals with a pathogenic germline variant in *DICER1*. *J Clin Oncol* 2019;37:668–76.
- Guillerman RP, Foulkes WD, Priest JR. Imaging of DICER1 syndrome. *Pediatr Radiol* 2019;49:1488–505.
- Foulkes WD, Priest JR, Duchaine TF. *DICER1*: mutations, microRNAs and mechanisms. *Nat Rev Cancer* 2014;14:662–72.
- Anglesio MS, Wang Y, Yang W, et al. Cancer-associated somatic *DICER1* hotspot mutations cause defective miRNA processing and reverse-strand expression bias to predominantly mature 3p strands through loss of 5p strand cleavage. *J Pathol* 2013;229:400–9.

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Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with prominent signet ring cell-like plasmacytic differentiation: a diagnostic challenge in small endoscopic biopsy



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To the Editor,

Signet ring cell features can be observed in various types of neoplasms, including epithelial, mesenchymal, and melanocytic tumours. However, lymphoma exhibiting signet ring cell morphology is rare and has been described as a morphological variant in several types of non-Hodgkin lymphomas.¹ To the best of my knowledge, signet ring cell morphology in marginal-zone lymphoma has not been previously documented.

I report the case of a 62-year-old male who underwent oesophago-gastroduodenoscopy (EGD) during a routine health screening at a local clinic, where atypical cells were identified. He was subsequently referred to our institution for further evaluation. The initial biopsy specimen, a superficial sample of the gastric mucosa, demonstrated significant glandular loss and diffuse infiltration of signet ring cell-like atypical cells within the lamina propria. These cells exhibited eccentrically located nuclei while maintaining overall nuclear contours, and

they lacked the crescent-shaped nuclear morphology typically associated with classical signet ring cells. No intracellular mucin accumulation was observed, and lymphoid aggregation was absent.

Immunohistochemical staining revealed that the signet ring cell-like cells were positive for leucocyte common antigen (LCA), CD20, and CD138 but negative for cytokeratin (CK). Based on these findings, mucosa-associated lymphoid tissue lymphoma was rendered, and a deep biopsy was recommended to establish a definitive diagnosis.

A follow-up endoscopic biopsy targeted a flat, erythematous lesion approximately 4 cm in diameter in the gastric midbody, yielding a more substantial sample. Histology revealed small atypical lymphoid cells infiltrating the deeper mucosa, whilst the superficial mucosa again showed diffuse infiltration of signet ring cell-like cells, consistent with the findings of the initial biopsy.

The patient reported mild weight loss over the preceding months but denied gastrointestinal symptoms. His complete blood count was within normal limits, and no atypical peripheral blood cells were observed.

Microscopic examination confirmed proliferation of signet ring cell-like and small lymphoid cells in the lamina propria. Numerous vacuolated cells infiltrated between gastric glands. Lymphoepithelial

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