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Prevalence of lung cysts in adolescents and adults with a germline *DICER1* pathogenic/likely pathogenic variant:

A report from the National Institutes of Health and International Pleuropulmonary Blastoma/*DICER1* Registry

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CONTRIBUTORSHIP

ATN, LMV, KAPS, and DRS take full responsibility for the content of the manuscript including the data and analyses. All authors contributed to the design of the study. ATN, LMV, AKH, LAH, AGC, NF, KNH, AL, YHM, DAH, KAPS, and DRS contributed to the acquisition of data. ATN, LMV, DW, AKH, KAPS, and DRS contributed to the development of the analysis plan. ATN, LMV, and DW performed the analysis. ATN, LMV, JK, AFB, and KNH contributed to data visualization. All authors contributed to the interpretation of data. ATN, LMV, KAPS, and DRS drafted the manuscript. DAH, KAPS, and DRS supervised the study. All authors critically revised the manuscript and approved the final version for submission.

COMPETING OF INTERESTS

Dr. Hill is owner of ResourcePath LLC, a company which does research and development of laboratory tests including for DICER1-related cancers. That work is unrelated to the information presented in this article. Dr. Stewart provides telegenetics services for Genome Medical, Inc, in accordance with relevant National Cancer Institute policies. The remaining authors have no conflicts to disclose.

ETHICS APPROVAL

This study involves human participants and was approved by the Institutional Review Board of Children's Minnesota (1611-130, 1111-112 and 1107-072) and National Cancer Institute (11-C-0034).

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Abstract

BACKGROUND: Pleuropulmonary blastoma (PPB), the hallmark tumor associated with *DICER1*-related tumor predisposition, is characterized by an age-related progression from a cystic lesion (type I) to a high-grade sarcoma with mixed cystic and solid features (type II) or purely solid lesion (type III). Not all cystic PPBs progress; type Ir (regressed), hypothesized to represent regressed or non-progressed type I PPB, is an air-filled, cystic lesion lacking a primitive sarcomatous component. This study aims to evaluate the prevalence of non-progressed lung cysts detected by computed tomography (CT) scan in adolescents and adults with germline *DICER1* pathogenic/likely pathogenic (P/LP) variants.

METHODS: Individuals were enrolled in the NCI Natural History of *DICER1* Syndrome study, the International PPB/*DICER1* Registry, and/or the International Ovarian and Testicular Stromal Tumor Registry. Individuals with a germline *DICER1* P/LP variant with first chest CT at 12 years of age or older were selected for this analysis.

RESULTS: In the combined databases, 110 individuals with a germline *DICER1* P/LP variant who underwent first chest CT at or after the age of 12 were identified. Cystic lung lesions were identified in 38% (42/110) with a total of 72 cystic lesions detected. No demographic differences were noted between those with lung cysts compared to those without lung cysts. Five cysts were resected with 4 centrally reviewed as type Ir PPB.

CONCLUSION: Lung cysts are common in adolescents and adults with germline *DICER1* variation. Further study is needed to understand the mechanism of non-progression or regression of lung cysts in childhood to guide judicious intervention.

INTRODUCTION

DICER1-related tumor predisposition (MONDO: 0100216) is an autosomal-dominant disorder caused by germline *DICER1* pathogenic variants that increase risk for a spectrum of benign and malignant tumors. The prevalence of loss-of-function variants in *DICER1* is estimated at 1:10,600.[1] Penetrance is incomplete, and many individuals are otherwise healthy or have minor manifestations of *DICER1*-related tumor predisposition such as benign thyroid nodules.[2] The study of families with a history of pleuropulmonary blastoma (PPB) in childhood prompted the sentinel discovery of its association with *DICER1* pathogenic variants in 2009.[3] The spectrum of neoplasms associated with *DICER1* pathogenic variants includes those of the lung, brain, kidneys, female genitourinary tract, and peritoneum, among others.[4]

Pleuropulmonary blastoma is the most common malignant lung tumor in infancy and early childhood and is the hallmark tumor associated with *DICER1*-related tumor predisposition. More than 70% of PPBs arise in individuals with a germline *DICER1* pathogenic variant.[5]

Nearly all PPBs have biallelic *DICER1* pathogenic variants, classically a loss-of-function variant and a missense variant in the RNase IIIb domain termed the "hotspot."[5–7] PPB may progress from a multilocular, cystic lesion (type I PPB) to a high-grade primitive multipatterned sarcoma, either mixed cystic and solid (type II PPB) or exclusively solid (type III PPB).[8] Not all cystic PPBs progress through these stages; many remain an architecturally multicystic or unilocular lesion without a primitive small cell population. This lesion, designated type Ir (regressed) PPB, is hypothesized to represent regressed or non-progressed type I PPB as primitive undifferentiated blastemal cells are usually histologically visible in type I PPB. Type Ir PPBs are found over a large age range and have been pathologically-confirmed in individuals as young as two months and up to the age of 45 years, in contrast to type I-III PPB which present before the age of 7 years in most cases.[6,7]

Outcome and pathologic features of type I-III PPB are well established.[6,7] Type Ir PPB presents a unique challenge as it is histologically distinct from type I PPB, lacking primitive malignant cells, but radiographically indistinguishable. Clinical factors such as age may suggest whether type I or Ir PPB is more likely. In the largest study of type I and Ir PPB, type Ir was frequently found incidentally and was more often unilocular and smaller by imaging in comparison to type I ($p < .001$).[6] Progression from type I to type II to type III PPB is well established, however, risk of progression of type Ir PPB is not well known. In a recent cohort of 87 individuals with type Ir PPB, two children with resected type Ir PPB later developed ipsilateral type III PPB.[6] Our observations thus far show that lung cysts, often representing type Ir PPB, are common in individuals with a germline *DICER1* pathogenic variant and may be detected at time of first chest computed tomography (CT) scan regardless of age though prevalence has not yet been definitively established. Individuals with mosaicism for variants in the RNase IIIb domain are known to have more sites of involvement than individuals with germline loss-of-function variants and have been found to have numerous lung cysts.[5,9]

In this study, we sought to determine the prevalence and characteristics (i.e., location, size and focality) of lung cysts in adolescents and adults with germline *DICER1* pathogenic/likely pathogenic variants to guide assessment of risk for progression.

METHODS

Individuals were enrolled in the NCI Natural History of *DICER1* Syndrome study (ClinicalTrials.gov identifier: NCT01247597), the International PPB/*DICER1* Registry (ClinicalTrials.gov identifier: NCT03382158), and/or the International Ovarian and Testicular Stromal Tumor (OTST) Registry (ClinicalTrials.gov identifier: NCT01970696). All study procedures were approved by the relevant human subjects committees and written informed consent (including assent when applicable) was obtained.

In the NCI Natural History of *DICER1* Syndrome study (NCI *DICER1* study), patients enrolled, and their biological relatives were recruited and tested for *DICER1* pathogenic/likely pathogenic (P/LP) variants. The proband was defined as the individual enrollee through whom each family was ascertained. Non-probands are family members of the

proband found to have the familial *DICER1* variant. For all participants (i.e., probands, non-probands with a P/LP variant and family member controls documented or presumed to be negative for a germline P/LP *DICER1* variant) medical records, pathology findings, imaging findings and questionnaires were systematically abstracted. As part of the study, select participants were invited to a 3-day evaluation at the NIH Clinical Center which included imaging and physical examination.

For participants in the International PPB/*DICER1* Registry and OTST Registry (the Registries), medical records, imaging studies and pathology samples were requested from treating institutions. Pathology samples were centrally reviewed as a part of Registry procedures (LPD and DAH). Germline *DICER1* results were abstracted from treatment records, when available, and in some cases tested through the Registries. *DICER1* P/LP variants were classified by type, with large deletions defined as deletion of multiple exons.

Individuals from the NCI *DICER1* study and the Registries with chest CT scans available for review and a known germline *DICER1* P/LP variant were selected for this analysis. Additionally, to ensure results were not biased toward individuals previously found to have lung cysts and to exclude individuals still at risk for progression to types II or III PPB, this analysis focuses on individuals without prior history of PPB whose first chest CT was performed at age 12 years or older. Additionally, individuals with mosaicism for *DICER1* RNase IIIB domain variants were excluded from analysis. All CTs were centrally reviewed (AL and KNH) and abstracted into standardized forms that included number of cysts, and for each cyst: laterality, lobe, size and septations. For Registry patients, distance from the pleura and indication for CT imaging was also ascertained. Enrollment in more than one study was possible; data fields for each participant were reconciled prior to analysis.

Demographic data was described with standard statistics. Cyst size was summarized using the volume of an ellipsoid (0.5236*length*width*height). Associations with presence of lung cyst were assessed using the χ^2 test and the Mann-Whitney test for categorical and numeric data, respectively. R (version 4.1.0) package trackViewer was used to create a lollipop plot to map *DICER1* P/LP variants along the *DICER1* gene. The heat maps of lung cyst volume were created as follows: Log10-transformed volume across all lung regions was aligned to a 1000-point sequential color scheme (https://colorbrewer2.org/) by matching the largest and smallest observed volumes with the darkest and lightest colors, respectively, and the remaining 998 color values with 998 equally-spaced intermediate volumes. Within each lung region, the observed cyst volumes were sorted and mapped to the nearest heatmap scale volumes, and a gradient fill for that region was constructed in Adobe Illustrator with equally-spaced gradient points corresponding to the appropriate heatmap colors. Gradient locations of the region's volume quartiles were annotated with lines.

RESULTS

Of 110 eligible participants with a germline *DICER1* P/LP variant whose first chest CT was obtained at 12 years of age or older, cystic lung lesions were identified in 38% (42/110) (95% CI: 29.6 – 47.5%) (Table 1). Median age at first CT scan was 33 years (range 12–73); 68% (75/110) were female. Indication for CT included research protocol in

73% (80/110), staging evaluation for other *DICER1*-related malignancy in 20% (22/110), routine surveillance related to germline *DICER1* P/LP variant in 5% (6/110), and pulmonary symptoms in 2% (2/110). One patient with pulmonary symptoms presented with chronic cough; CT findings suggested chronic indolent small airway infection which was felt to be the cause of the cough (a 1.1 cm lung cyst in the right apex was deemed unlikely to be related to the cough). The other patient with pulmonary symptoms presented with shortness of breath and was not found to have a lung cyst on CT. Thus, all radiographic findings related to detection of the cysts were incidental with no apparent complications related to the lung cysts.

Half (55/110) of individuals had nonsense variants. Fig. 1A represents a distribution of variants within the *DICER1* gene for both individuals with a lung cyst and those without, whereas in Fig. 1B one family member was randomly selected and represented on the plot to control for a possible family effect. In other words, by displaying one member per family the risk of exaggerating the effect of *DICER1* on lung cyst formation due to an unidentified familial effect was mitigated. There was no statistical difference in distribution of type of *DICER1* P/LP variant in individuals with lung cysts compared to those without ($p = .475$) although the non-significant result may be due to rare variant types and small sample size as the rate of nonsense variants was 62% in those with a lung cyst versus 43% in those without.

A total of 72 cystic lesions were identified (Table 2). Septations were noted in 8% (6/72). Representative cross-sectional imaging is provided for both unilocular (Fig. 2A) and multiseptated (Fig. 2B) lung cysts. For patients with data available, more than half of the cysts involved or abutted the pleura with a median distance to the pleura of 0 cm (range: 0 – 2.3 cm) (n=17). Fifty-eight percent (42/72) of cysts were right-sided. The mean number of cysts per patient was 1.7 (median 1). A single individual had 10 cysts identified (Fig. 3). Otherwise, no individual had more than 5 lung cysts. Imaging for the individual with 10 cysts occurred at 65 years of age with medical history noted to include rheumatoid arthritis and Sjögren syndrome. Both rheumatoid arthritis and Sjögren syndrome have been implicated in cystic lung changes in rare reports; it is unclear if these contributed to the patient's imaging findings. [10,11]

When considering the largest cyst per patient (n=42), median maximum dimension was 1.7 cm (range: 0.6 – 14.4 cm) and median volume was 1.65 cm^3 (range: 0.08 – 823.73 cm^3). When considering each cyst individually (n=72), the median maximum dimension was 1.2 cm (range: 0.3 – 14.4 cm) and median volume was 0.66 cm^3 (range: 0.01 – 823.73 cm^3). A color heatmap (Fig. 4) illustrates the distribution of lung cysts by lobe (not specific location within each lobe) and size.

Of the individuals with lung cysts, 5 underwent resection. Central pathology review was available for all cases. Four were type Ir PPB and one was centrally reviewed as apical fibrosis with an underlying bulla. This bulla was felt to represent a separate process, not related to the individuals underlying germline *DICER1* P/LP variant. The reason for resection was ascertained from clinical documentation and included: 1) concern for progression of PPB, 2) concern for congenital pulmonary adenomatoid malformation, 3) large size of the cyst, and 4) elective surgery in two individuals whose siblings had advanced

PPB. The median age of the individuals who underwent resection of a lung cyst was 14 years (range: 12 – 24 years) compared to 34 years (range: 12 – 72 years) for individuals with a lung cyst(s) that did not undergo resection ($p = .010$). Additionally, the median maximum dimension of the largest cyst for those undergoing resection was 11.1 cm (range: 2 – 14.4 cm) compared to 1.6 cm (range: 0.6 – 11.6 cm) for individuals with a lung cyst(s) that did not undergo resection ($p = .002$). Most individuals did not undergo repeat chest CT imaging.

DISCUSSION

This report provides the most comprehensive quantitative analysis to date of the prevalence of lung cysts in adolescents (≥12 years of age) and adults with germline *DICER1* P/LP variants. We highlight the potential for lung cysts to prompt recognition of *DICER1*-related tumor predisposition, especially when noted in the context of personal or family history of childhood cancer, macrocephaly, thyroid nodules or other *DICER1*-related conditions. [12,13] These findings suggest that lung cysts are among the most common manifestations in an individual with a germline *DICER1* P/LP variant along with thyroid disease including multinodular goiter.[13]

We found no identifiable demographic difference between individuals with *DICER1* P/LP variants with and without a lung cyst. Prior studies from our combined groups have quantified the prevalence of lung cysts in patients with *DICER1* P/LP variant as 43%, in one study reported based on unpublished data, and 28% in a neoplasm assessment risk study in non-probands with germline *DICER1* P/LP variants. [2,5]

Our current study strengthens prior findings with the largest cohort analyzed to date with strict inclusion criteria to limit ascertainment bias and with central radiology review of all chest CTs. In this report, we excluded individuals with their first CT scan prior to the age of 12 years, as individuals with lung cysts identified prior to age 12 who did not undergo resection were more likely to have repeat cross-sectional imaging and inclusion may have overestimated the prevalence of lung cysts. The minimum age for this study was chosen based on previously published Registry data as the risk of progression to type II or III PPB after age 12 is very small and nearly all type I-III PPB are diagnosed by the age of 7, although few cases of type I PPB have been identified up to the age of 12.[6,7] Additionally, individuals with mosaicism for RNase IIIb variants were excluded due to higher risk for lung cysts and other manifestations of *DICER1*-related tumor predisposition.[5,9]

Our study supports that lung cysts, generally representing type Ir PPB, are common in adolescents and adults with germline *DICER1* P/LP variants. The mechanism of regression or non-progression remains unknown and further studies are needed to elucidate the biology of progressed vs. non-progressed/regressed PPB. *TP53*, a tumor suppressor gene, may have a role in progression to type II and III PPB as suggested in earlier studies.[14,15] Development of biomarkers has the potential to assess for progression of disease, and work is underway to validate circulating tumor DNA findings throughout the disease course in patients with PPB.

Future elucidation of factors that contribute to progression/regression will aid in predicting progression or early detection of progression and may help guide judicious surgical intervention. Although of high clinical interest, specific estimation of risk of progression is particularly challenging with available data. While nearly 40% of adolescents and adults with germline *DICER1* P/LP variants have lung cysts and advanced PPB is rare, it remains unclear if progression to advanced PPB is driven by genetics, environmental factors, randomness or a combination.

Although definitive numbers are not available for the incidence of advanced PPB each year, types II and III PPB are certainly rare with fewer than 20 cases per year in the United States. Based on the prevalence of lung cysts reported in this study as well as the estimated prevalence of germline *DICER1* P/LP variants it seems that the risk of progression of a lung cyst is low, although this should be approached with caution.[1] By definition, our study excluded patients with PPB resected prior to age 12. Imaging characteristics such as size and presence of septations, as well as age at diagnosis have been shown to be helpful in differentiating type I from Ir PPB and may help guide decision making.[6] Monitoring cysts from infancy would provide further insight, but given the poor outcomes of type II and III PPB, early surgical intervention for cysts thought to represent type I PPB is recommended, therefore these data are not available. While all surgery carries risk, generally surgeries for type I and Ir PPB are well tolerated. [6]

The approach to cystic lesions concerning for PPB will vary based on age, presenting symptoms, size and radiographic appearance. Data from the Registry suggests that almost all progression of PPB occurs prior to the age of 7 years, with type II and III PPB carrying a poor prognosis.[7] The challenge remains to balance the need to prevent progression to types II and III PPB with the desire to avoid unnecessary surgery in individuals with low risk of progression. When attempting to differentiate type I from Ir PPB, a predictive model was developed based on cyst size and age, with an increased probability of a cystic lesion being a type Ir at older age (greater than 2.5 years) and smaller size (less than 3 cm), although there was still substantial overlap in the cohorts.[6]

Progression from type I to types II and III PPB is well established and a substantial clinical concern although it remains unclear if an unresected type Ir PPB has the potential to progress.[6,8] Two children with an initial type Ir diagnosis have later progressed to advanced PPB, both diagnosed at 2 years.[6] Whether this represents an undiagnosed primitive malignant component or an adjacent, unresected area of metachronous PPB in an “at risk field” is unknown and is the subject of ongoing preclinical work.

For a subset of participants in this analysis, we were able to measure and report lung cyst distance from the pleura. More than half of lung cysts were abutting the pleura with a possible risk for spontaneous pneumothorax. While pneumothorax is a common presenting symptom of cystic PPB in childhood, seen in nearly one third of patients with type I PPB, pneumothorax is less common in older individuals with type Ir PPB.[6] Still, individuals with known lung cysts should be counseled regarding potential risks for pneumothorax.

When considering surgery versus observation in childhood, assessment of risk for development of new lung cysts and ensuring adequate future lung function are important considerations. While outside the scope of this analysis, our unpublished observations suggest that most lung cysts related to germline *DICER1* loss-of-function variants develop very early in life with a small subset detected prenatally and lower risk for new cyst development after age 4 years. Although type I PPB has been noted prenatally, congenital pulmonary airway malformations (CPAM) are a more common prenatal finding.[8,16] For clinicians, preoperatively distinguishing cystic PPB from benign cystic lesions remains challenging.[16–18]

We noted a predominance of females in our dataset, many of whom had a chest CT in the context of staging evaluation for malignancies of the female genitourinary tract. Sertoli-Leydig cell tumor and cervical embryonal rhabdomyosarcoma are well-documented manifestations of *DICER1*-related tumor predisposition.[19,20] These findings are in accordance with increased prevalence of neoplasms in females (26.5%) versus males (10.2%) by age 50 years based on a prior study of non-probands. [2] The excess in females is largely due to increases in endocrine organ neoplasms involving the thyroid gland, uterus and ovaries.

Surveillance recommendations are available for individuals with known germline *DICER1* P/LP variants.[21] The screening for PPB in individuals with germline *DICER1* P/LP variants includes chest X-ray at birth and every 6 months until age 8, then yearly through age 12. Recommendations also include chest CT at age 3–6 months and again at age 2–2.5 years. Prenatal ultrasound for detection of lung cysts may also be considered in the third trimester when the mother or father is known to have a germline *DICER1* P/LP variant. For individuals with a variant detected after the age of 12, baseline chest imaging with either chest X-ray or chest CT should be considered. Surveillance recommendations may facilitate early detection of PPB which is associated with a more favorable prognosis.[22] In a recent analysis of patients with type I and Ir PPB, 4 patients with type I PPB and 26 patients with resected type Ir PPB were detected with routine surveillance for germline *DICER1* P/LP variant or family history.[6] Given the high prevalence of lung cysts in individuals with germline *DICER1* P/LP variants, identification of lung cysts on imaging should prompt careful attention to personal and family medical history and consideration for *DICER1* testing. Findings of multiple lung cysts, especially if seen in conjunction with renal cysts and/or intestinal polyps, should raise the question of mosaicism for *DICER1* even if blood or buccal testing is negative.

Although we highlight our findings of *DICER1*-related lung cysts, other inherited conditions are also associated with lung cysts such as Birt-Hogg-Dubé, Marfan syndrome and Filamin A deficiency.[23–26] Congenital causes of cystic lung changes include CPAM, pulmonary sequestration, and bronchogenic cysts, among others. These should all be considered in the differential diagnosis of children and adults with lung cysts identified by imaging.

Strengths of this analysis include the largest cohort of patients with germline *DICER1* P/LP variants pooled from multiple studies with each CT scan centrally reviewed by a study radiologist. Limitations include limited size of the cohort, risk for ascertainment bias (e.g.

individual or family history of tumor prompting genetic testing and study enrollment) and limitations in natural history data especially for those cysts which presented early and were resected. An additional limitation is the absence of histologic confirmation that cysts were type Ir PPB as only five patients underwent resection. Nonetheless, this analysis provides important information regarding the prevalence of lung cysts in adolescents and adults with germline *DICER1* P/LP variants. To date, apart from the issue of mosaicism, assessment of variant type and resulting phenotype in *DICER1*-related tumor predisposition has not been studied. Although challenging in rare diseases, genotype-phenotype correlation along with study of variant type and location may provide further insight into lung cyst development as well as other *DICER1*-related conditions and this analysis is underway.

While this manuscript adds to our understanding of lung cysts in individuals with *DICER1*, further longitudinal study regarding progression, pneumothorax and other complications is needed and is underway. We hope that treating physicians and individuals with these conditions will continue to participate in research so that further data may be collected to more definitely inform care. The International PPB/*DICER1* Registry remains available as a resource for patients and health care professionals and provides free central pathology and radiology review (www.ppbregistry.org).

In conclusion, lung cysts are common in adolescents (≥12 years of age) and adults with germline *DICER1* P/LP variants. Despite the known risk for progression of lung cysts detected in early childhood, no progression events were observed in this cohort of adolescents and adults. Further study is needed to understand the mechanism of non-progression or regression of lung cysts in childhood to guide judicious surgical intervention.

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DATA SHARING

Data are available upon reasonable request.

Abbreviations:

CPAM	congenital pulmonary airway malformation
CT	computed tomography

NCI DICER1 Study	NCI Natural History of *DICER1* Syndrome Study
OTST	Ovarian and Testicular Stromal Tumor Registry
P/LP	Pathogenic/likely pathogenic
PPB	pleuropulmonary blastoma
Registries	International PPB/*DICER1* Registry and OTST Registry

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What is already known on this topic

- *DICER1*-related tumor predisposition is associated with a spectrum of benign and malignant tumors in children and young adults including pleuropulmonary blastoma (PPB) and ovarian tumors.
- PPB is characterized by an age-related progression from a cystic lesion (type I PPB) to a high-grade sarcoma with mixed cystic and solid features (type II PPB) or purely solid lesion (type III PPB) although not all lesions progress. A subset of cystic lesions represent type Ir (regressed) PPB which lacks a malignant component.

What this study adds

- In the largest, most comprehensive study of its type, we quantify the prevalence of lung cysts, thought to represent type Ir PPB, in adolescents (≥12 years of age) and adults and establish lung cysts as one of the most common manifestations in individuals with germline *DICER1* pathogenic/likely pathogenic (P/LP) variants.

How this study might affect research practice or policy

- Surveillance for PPB in individuals with germline *DICER1* P/LP variants includes chest X-ray at birth and every 6 months until age 8, then yearly through age 12. Chest CT is currently recommended at 3–6 months of age and again at 2–2.5 years of age. After the age of 12, baseline chest imaging may be considered.
- Identification of lung cysts may serve as an entry point to *DICER1* testing and surveillance and help facilitate early detection of *DICER1*-associated tumors in their earliest form in probands and family members.
- These findings lay the groundwork for further studies of the mechanism of non-progression or regression of *DICER1*-related lung cysts in childhood.

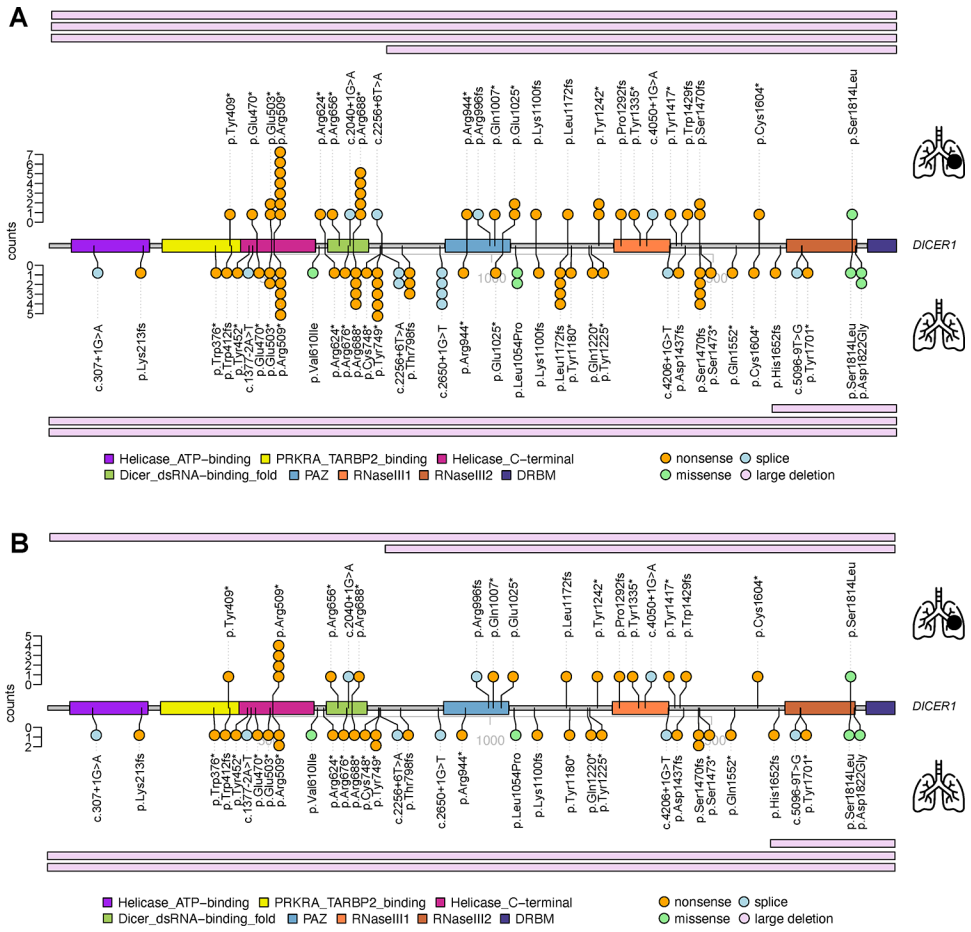

Figure 1:

Lollipop plot of variant distribution within the *DICER1* gene among participants with (top) and without (bottom) lung cysts for all participants **(A)** and one randomly selected family member **(B)**.

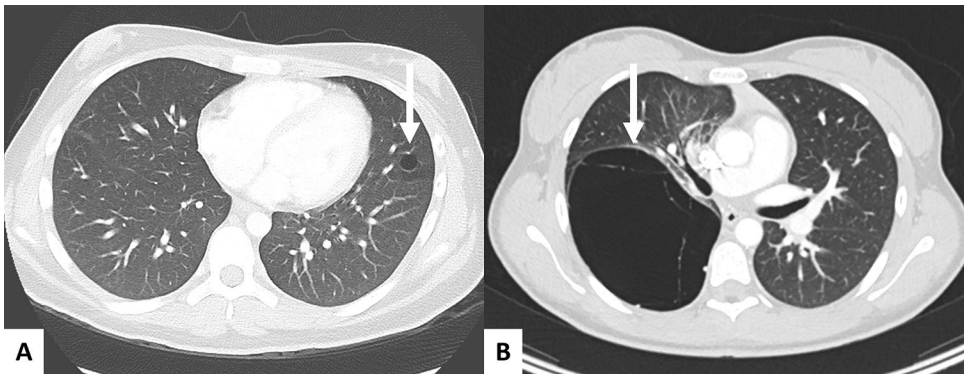

Figure 2:

Representative cross-sectional imaging of lung cysts. **(A)** Unilocular cyst (white arrow) in the lingula of an adolescent. **(B)** Multiseptated cyst (white arrow) in the right upper lobe of an adolescent, resected and diagnosed as type Ir pleuropulmonary blastoma.

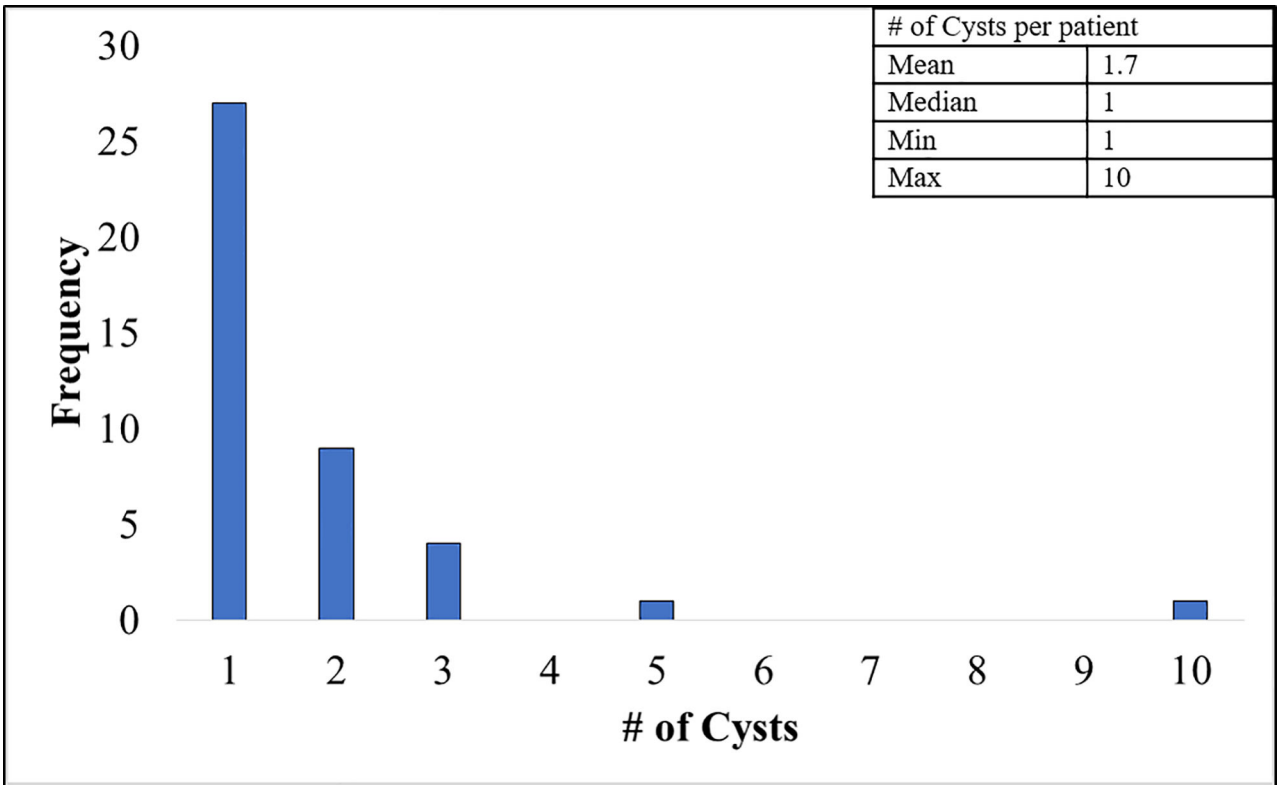

Figure 3:
Histogram of number of cysts per participants with lung cysts (n = 42).

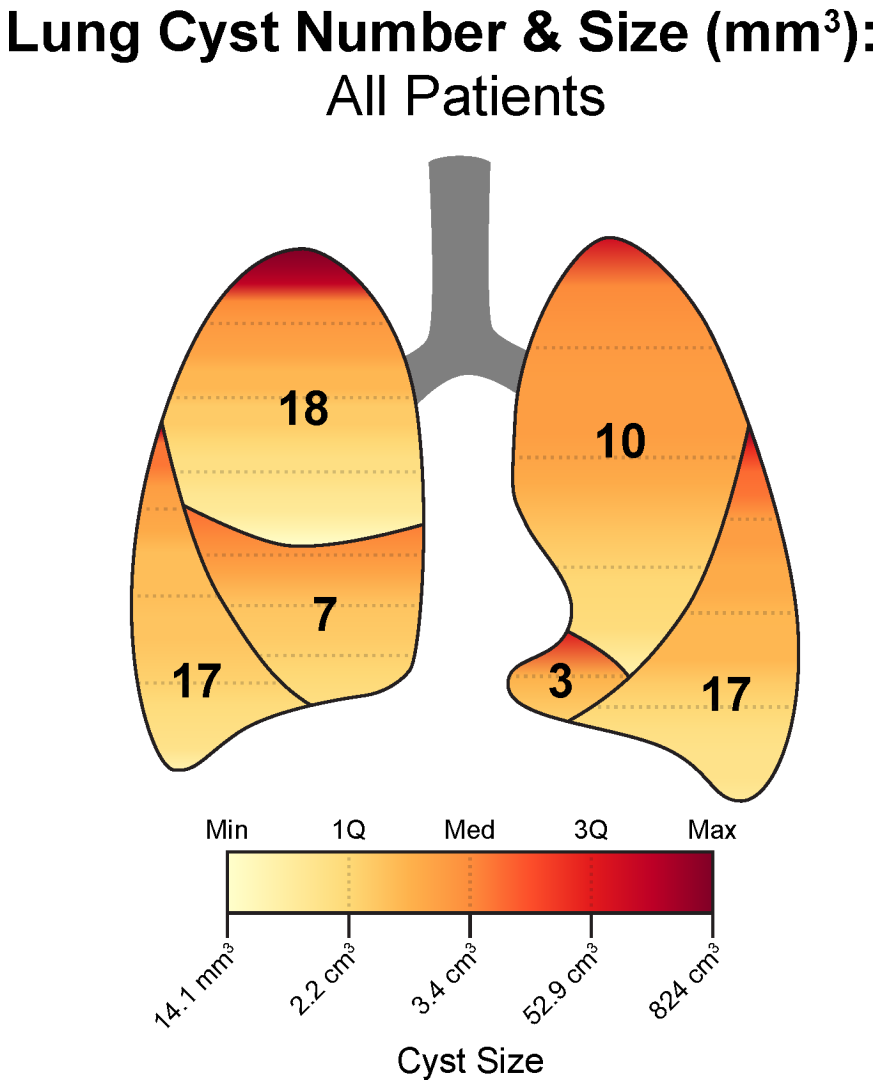

Figure 4:
Color heatmap with distribution of all lung cysts by lung lobe origin and size of cyst (n = 72).

Table 1:

Characteristics of participants with and without lung cysts.

Variable	Individuals with lung cyst(s) (n=42) n/N (%)	Individuals with no lung cyst (n=68) n/N (%)	*P*-value	Total (n=110) n/N (%)
Age at CT, median [range], years	33 [12 – 72]	33 [12 – 73]	.379	33 [12 – 73]
Sex				
Female	26/42 (62)	49/68 (71)	.267	75/110 (68)
Male	16/42 (38)	19/68 (29)		35/110 (32)
Reason for CT				
-Study procedure	30/42 (71)	50/68 (74)		80/110 (73)
-Other Malignancy	8/42 (19)	14/68 (21)	.914	22/110 (20)
-*DICER1*workup	3/42 (7)	3/68 (4)		6/110 (5)
-Pulmonary Symptoms	1/42 (2)	1/68 (1)		2/110 (2)
Germline *DICER1*P/LP Variant				
-Nonsense	26/42 (62)	29/68 (43)		55/110 (50)
-Deletion	5/42 (12)	10/68 (15)		15/110 (14)
-Splice Site	4/42 (10)	9/68 (13)		13/110 (12)
-Large Deletion	4/42 (10)	3/68 (4)		7/110 (6)
-Missense	1/42 (2)	6/68 (9)	.475	7/110 (6)
-Insertion	1/42 (2)	4/68 (6)		5/110 (5)
-Duplication	1/42 (2)	3/68 (4)		4/110 (4)
-Deletion/Insertion	0/42 (0)	1/68 (1)		1/110 (1)
-Intronic	0/42 (0)	1/68 (1)		1/110 (1)
-Unknown	0/42 (0)	2/68 (3)		2/110 (2)

CT, computed tomography; P/LP, pathogenic/likely pathogenic

Table 2:

Characteristics of identified lung cysts.

Variable	Individuals with lung cyst (n=42) n/N (%)
No. Lung Cysts, median [range]	1 [1–10]
Septations on CT	6/72 (8)
Distance from pleura, median [range], cm	0 [0 – 2.3] (n=17)
Laterality	
Right	**42/72 (58)**
RUL	18/72 (25)
RML	7/72 (10)
RLL	17/72 (24)
Left	**30/72 (42)**
LUL	10/72 (14)
Lingula	3/72 (4)
LLL	17/72 (24)
Largest cyst per patient – measurements	
Max Dimension, median [range], cm	1.7 [0.6–14.4] (n=42)
Volume, median [range], cm^3	1.65 (0.08–823.73] (n=42)
All cysts - measurements	
Max Dimension – overall, median [range], cm	1.2 [0.3–14.4] (n=72)
Volume – overall, median [range], cm^3	0.66 [0.01–823.73] (n=72)
Outcome	
Participants with resection	5/42 (12)

CT, computed tomography, LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe