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Nasal chondromesenchymal hamartomas in a cohort with pathogenic germline variation in *DICER1**

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Abstract

Background: Nasal chondromesenchymal hamartomas are benign, rare nasal tumors associated with *DICER1* pathogenic germline variation. They can be locally destructive and recurrent if not completely resected.

Methodology: In this single-center, case-control study, otorhinolaryngology evaluations and review of systems questionnaires of *DICER1*-carriers and controls enrolled in the *DICER1* Natural History Study at the National Cancer Institute were collected. Review of these medical records were analyzed to determine if *DICER*1-carriers experienced different sinonasal clinical manifestations compared to controls. Additionally, the number of diagnoses of nasal chondromesenchymal hamartoma cases in the NCI *DICER1* study was compared against the total person years of observation of *DICER1*-carriers in the study to determine the total number of cases per person-years of observation. Lastly, both the NCI *DICER1* study and the International Pleuropulmonary Blastoma/*DICER1* Registry were queried for unpublished cases of nasal chondromesenchymal hamartomas.

Results: There were no clinical differences in sinonasal symptomatology between *DICER1*-carriers and control patients seen in the ENT clinic. We observed of two cases of nasal chondromesenchymal hamartoma in a total of 555 person-years of monitoring *DICER1*-carriers. We include six unpublished nasal chondromesenchymal hamartoma cases. When combined with a comprehensive literature review, 38% of nasal chondromesenchymal hamartoma cases had at least one additional *DICER1*-associated tumor and 24% of the NCMH were found in the ethmoid sinus, the most commonly involved paranasal sinus.

Conclusions: We quantify the risk of developing nasal chondromesenchymal hamartomas in our cohort of 236 *DICER1*-carriers, report six unpublished cases, and provide an updated review of the literature.

Key words: *DICER1*, nasal chondromesenchymal hamartoma, microRNA, pleuropulmonary blastoma

Trial registration: *DICER1*-related Pleuropulmonary Blastoma Cancer Predisposition Syndrome: A Natural History Study" (National Cancer Institute (NCI) Protocol 11-C-0034; NCT01247597) https://clinicaltrials.gov/ct2/show/NCT01247597; "International Pleuropulmonary Blastoma (PPB)/*DICER1* Registry" (NCT03382158) https://clinicaltrials.gov/ct2/show/NCT03382158; "International Pleuropulmonary Blastoma Treatment and Biology Registry" (NCT01464606); https://clinicaltrials.gov/ct2/show/NCT01464606.

Introduction

The *DICER1* gene encodes an RNase endonuclease that is required for the production of microRNAs [1]. Pathogenic germline *DICER1* variants give rise to an autosomal dominant tumor-predisposition disorder associated with an increased risk of a variety of benign and malignant tumors including pleuropulmonary blastoma (PPB), ovarian sex cord-stromal tumors, cystic nephroma, thyroid gland neoplasia, pituitary blastoma, pineoblastoma, and nasal chrondomesenchymal hamartoma [2]. Nasal chondromesenchymal hamartomas (NCMH) are rare tumors of the sinonasal tract. Usually diagnosed in young children or infants, the lesions have a complex histology that is comprised of mixed mesenchymal cells amongst other chondral and osseous elements [3]. Although typically benign in nature, the lesion can be locally invasive with potential intracranial or parasinus extension [4]. Surgical removal is the standard treatment; however, incomplete resection may be associated with recurrence of the mass [3].

NCMHs were first reported in 1998 in seven young children with non-obstructive, non-compressive nasal tract masses, amenable to surgical resection and similar in histology to previously described mesenchymal hamartoma of the chest wall [5]. Interestingly, this initial report identified one child with an NCMH and prior history of pleuropulmonary blastoma [5].

Since then, there have been over 50 cases of NCMH reported in the literature. To better understand the clinical presentation associated with NCMH, we investigated sinonasal signs and symptoms in *DICER1*-carriers and controls and the likelihood of developing NCMH. We quantified the risk of developing NCMH in our cohort of 236 *DICER1*-carriers, report six unpublished cases, and provide an updated review of the literature.

Materials and Methods

ENT clinic evaluation and review

In this report, we use the term "*DICER1*-carrier" for those individuals with a germline pathogenic *DICER1* variant, regardless of whether they have clinical findings. Family members who did not harbor a germline pathogenic *DICER1* variant served as controls.

To ascertain if *DICER1*-carriers were more likely to experience particular sinonasal symptoms or had unique physical exam findings which could be used as markers of clinical concern for the development of NCMH, medical records were reviewed from 111 *DICER1*-carriers and 81 family controls seen in the otorhinolaryngology clinic at the National Institutes of Health (NIH) Clinical Center as part of a comprehensive evaluation for participants enrolled in the "*DICER1*-related Pleuropulmonary Blastoma Cancer Predisposition Syndrome: A Natural History Study" (National Cancer Institute (NCI) Protocol 11-C-0034; NCT01247597). The relevant Institutional Review Board approved this study; all patients (and/or parents) gave written consent/assent to participate. Briefly, individuals were eligible if they or a family member harbored a germline pathogenic *DICER1* variant or had a *DICER1*-associated tumor. Germline *DICER1* testing was performed on all participants in this study. A subset of participants underwent a comprehensive three-day outpatient evaluation at the NIH Clinical Center, including imaging, laboratory testing and sub-specialty examination. *DICER1*-carriers and family controls were evaluated (history and physical exam and nasal endoscopy unless refused) by the same ENT physician. Clinical information was extracted from the chart including review of systems responses, physical exam findings and follow-up recommendations. Each patient's review of systems was recoded and divided into "yes" or "no" categories. As a longitudinal study, participants were mailed follow-up questionnaires every two years to inquire about the development of new pathology. Pathology materials were obtained whenever possible.

Statistical analysis

The Fisher's Exact test was used to determine statistically significant differences in the frequency of signs and symptoms of *DICER1*-carriers (including individuals with suspected *DICER1* mosaicism) and family controls.

Incidence determination

The number of years between enrollment of subjects into the NCI *DICER1* Study and either the development of an NCMH or the date of their last follow-up questionnaire or contact with the study coordinators was summed to calculate the total number of person-years of observation. This determination included *DICER1*-carriers in both the field and the clinical cohorts.

Literature review

A large systematic review of the literature cataloged the case reports and case series of NCMH up to 2015, including 48 individual cases [6]. We reproduced the search strategy querying PubMed and Google Scholar detailed in that paper to identify NCMH case reports 2015 through March 2019 (including one paper published in 2014 that was not included in the Mason et al. review) [4, 7-17].

New case collection

Both the NCI *DICER1* Study and the International PPB/*DICER1* Registry ("International Pleuropulmonary Blastoma [PPB]/*DICER1* Registry" NCT03382158); "International Pleuropulmonary Blastoma Treatment and Biology Registry" NCT01464606) were queried for unpublished cases of NCMH.

Results

ENT clinic evaluation results

Overall, there were no statistically significant differences in sinonasal symptoms or physical exam findings between *DICER1*-

Table 1. Demographics of 192 *DICER1*-carriers and control individuals.

Parameter	*DICER1*-Carriers n=111 (%)	Family Controls n=81 (%)
Age < 18 years[a]	50 (45%)	21 (26%)
Age ≥ 18 years[a]	61 (55%)	60 (74%)
Male[b]	52 (47%)	45 (55%)
Female[b]	59 (53%)	36 (44%)

[a] Fisher's exact test between *DICER1*-carriers and controls (p-value = 0.01); [b] Fisher's exact test between *DICER1*-carriers and controls (p-value = 0.25).

carriers and controls. One hundred and eleven *DICER1*-carriers and 81 family controls were evaluated in the ENT clinic from November 2011 through March 2017. The demographics of the *DICER1*-carriers and controls are outlined in Table 1. There was no significant difference in proportion of males and females in the *DICER1*-carrier and control groups. However, there was a greater number of *DICER1*-carriers less than 18 years old compared to the controls. There were no statistically significant differences in the frequency of sinonasal symptoms reported by *DICER1*-carriers versus controls (Supplementary Table 1).

Of the nasal endoscopy screening evaluations, 6% of the *DICER1*-carriers and 4% of the family controls had findings, including polyps, polypoid tissue or a yellow-colored rhinorrhea. Of those who had physical exam or nasal endoscopy findings, only one patient went on to have surgical evaluation and intervention (sFigure 1) and was found to have a *Bipolaris* species fungal infection. No NCMH was discovered during the ENT evaluations at the NIH. We did not find any sinonasal symptom or physical exam findings that was distinct to *DICER1*-carriers that could be used as a surrogate screening marker for NCMH development.

Incidence of NCMH in NCI cohort over period of evaluation. Since the inception of the NCI *DICER1* Study, 236 *DICER*-carriers were observed over 555 person-years in the Field and Clinical Center cohorts. During that time, two NCMH developed in two *DICER1*-carriers (cases 61 and 64 in Table 2) at 53 months and 84 months after evaluation at the Clinical Center, respectively, resulting in an incidence rate of two cases in 555 person-years. Both patients who developed NCMH underwent successful resection.

Table 2. Six unpublished cases of individuals with nasal chondromesenchymal hamartomas. Patient ages have been rounded to the nearest even number to protect personal privacy.

Case No.	Age at Presentation/ Gender	Side & Size	Symptoms	Site	Co-morbidity	Investigations[a,b]	Follow-up
64	10 years/F	Right	1. Nasal Congestion	1. Nasal Cavity 2. Nasopharynx	Medulloepithelioma, Thyroid Nodules[18]	ND	No recurrence at 5 months post resection
63	8 years/F	Left, Recurred in right	1st Presentation: 1. ND 2nd Presentation 1. Epistaxis 2. Obstruction	1. Nasal Cavity 2. Left sphenoid 3. Nasopharynx 4. Skull Base	Cystic nephroma, Rhabdomyosarcoma, PNET, Immature teratoma[19]	CT	Recurrence 30 months post; underwent resection
62	12 years/M	Right	1. Nasal congestion	1. Right maxillary sinus	PPB Type III	ND	No recurrence at 9 years post
61	8 years/M	Bilateral	1. Nasal obstruction 2. Chronic sinusitis	1. Nasal cavity 2. Left sphenoid 3. Ethmoid Sinus	PPB Type II	ND	2 Recurrences 6 -12 months after initial resection, underwent resection x2 – No recurrence 30 months after
60	8 years/F	Right, then Bilateral (multiple aggregates, largest 2.5 x 1.0 cm)	1. Chronic recurrent sinusitis 2. Chronic nasal congestion	1. Nasal Cavity 2. Right Sphenoid 3. Left Sphenoid	PPB Type II	CT, MRI	Recurrence at 23 months and 36 months. No recurrence at 9 years post.
59	10 years/F	Right	1. Snoring 2. Labored Breathing 3. Chronic Sinusitis	1. Nasal Cavity 2. Ethmoid Sinus	PPB Type III with Brain Metastases	CT	No recurrence after 11 years

ND = Not Documented; CT = Computed Topography scan; MRI = Magnetic Resonance Imaging; M = male; F = female; PPB = pleuropulmonary blastoma. [a] All patients were positive for a pathogenic germline *DICER1* variant, [b] All patients were treated with surgical resection.

Table 3. Location of nasal chondromesenchymal hamartomas in published and unpublished cases.

Location (64 Patients)	Number of NCMH at Location (%) (Total Tumors = 99)
Ethmoid	24 (24%)
Orbital	19 (19%)
Skull Base/Intracranial	20 (20%)
Maxillary	14 (14%)
Nasal Cavity Only	8 (8%)
Nasopharynx	4 (4%)
Sphenoid	1 (1%)
Frontal	1 (1%)
ND	8 (8%)

Percentage does not sum to 100% as one NCMH can be found in multiple locations; ND = Not Documented.

Literature review with new case reports

Systematic review of the literature identified 12 additional published cases of NCMH since Mason et al. and we present six unpublished cases of NCMH. Tables 2 and 3 are extensions of the systematic review published in 2015 [6] with published (Supplementary Table 2) [4,7-17] and unpublished (Table 2) [18, 19] cases from the NCI *DICER1* study and the International PPB/*DICER1* Registry through February 2019. In total, there were 58 cases of NCMH reported. Of these, 38% had at least one additional *DICER1*-associated tumor; eight patients had two or more *DICER1*-associated neoplasms. *DICER1* testing was reported in 17% of individuals in the systemic review by Mason et al., in 25% of patients of the subsequent literature review (Supplementary Table 2) and in 100% of the unpublished cases (Table 2). The median age of the patients in reported and unpublished cases presented was seven years old (range 0 days to 70 years old). Of the 64 cases reviewed 63% were male, 36% were female and 1% did not document the gender. While all cases involved the nasal cavity, the NCMH was more likely be present in the ethmoid sinus (24%) over other areas (Table 3). Two of the previously unpublished cases are outlined below, and two additional cases are presented in the Supplemental Information (clinical information for two cases was unavailable). The two cases in the body of this report highlight a complicated PPB presentation with NCMH seven years later and a case of recurrent NCMH requiring multiple resections.

For the following two cases, the chronological timeline has been generalized to protect patient privacy.

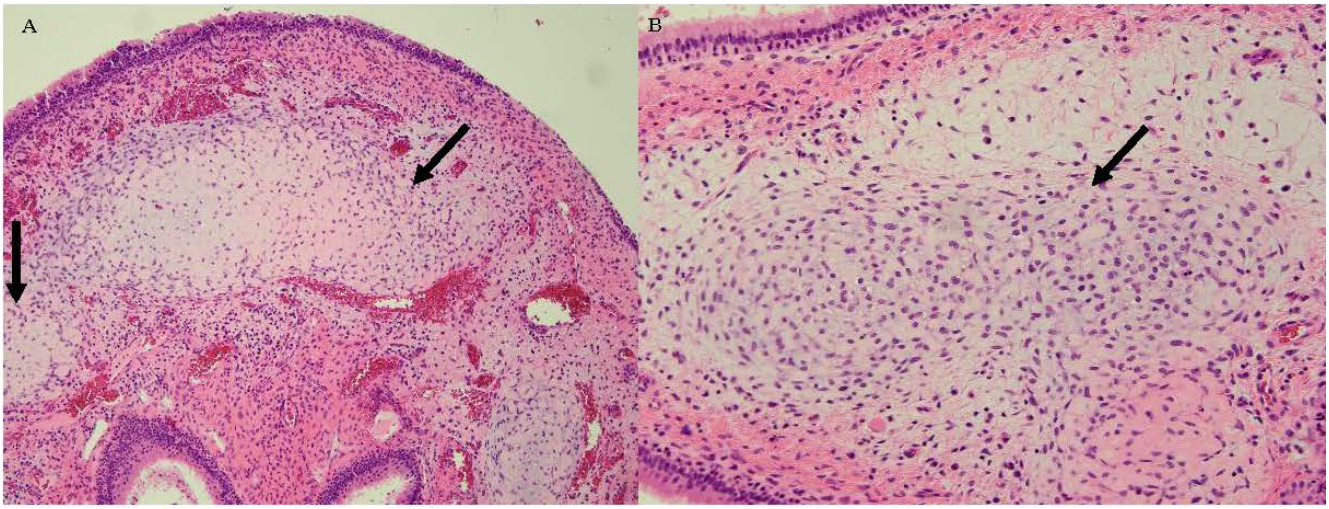
Case 59 in Table 2

A female child with germline *DICER1* c.2040+1G>T was diagnosed with a right PPB Type III and underwent a right lower lobe lobectomy and 43 weeks of adjunctive chemotherapy with doxorubicin, vincristine, cyclophosphamide, ifosfamide, topotecan and carboplatin. Several years later, she developed metastatic PPB in the right frontal lobe and underwent resection followed by 44 Gy of radiation. Her post-treatment issues include(d) chronic nasal congestion with snoring and chronic sinusitis, asthma, pneumonia and dysphagia. She had multiple computed topography and magnetic resonance imaging to evaluate the chronic congestion, the majority of which were negative until two months prior to the NCMH resection. That CT scan showed opacification of the sinuses with concern for polyposis. She had resection of the right nasal mass, subsequently diagnosed as NCMH. Since that time, she has had no further nasal symptoms, regrowth of the mass or additional concern for PPB recurrence. She remains well nearly 20 years after her PPB recurrence and over 10 years since her NCMH diagnosis with bilateral thyroid nodules and no other signs of *DICER1*-associated disease, and she is currently following published surveillance recommendations [20].

Case 60 in Table 2

A female with germline *DICER1* c.4407_4410delTTCT (p.Ser1470Leufs) was diagnosed as a young child with PPB Type II and underwent left lower lobectomy followed by 36 weeks of chemotherapy with ifosfamide, vincristine, dactinomycin and doxorubicin. She had a subsequent local relapse and was treated with carboplatin, etoposide, cyclophosphamide and radiation. Since the completion of therapy, she experienced chronic nasal congestion and chronic sinusitis. After several years, she was diagnosed with a right NCMH on CT scan and underwent endoscopic gross total resection. The lesion filled the right nasal cavity and extended from the skull base to the nasopharynx. Her symptoms recurred less than 6 months later at which time she had surveillance PPB surveillance imaging, including an MRI of the brain, which showed a left nasal mass, confirmed by nasal endoscopy. During the revision surgery, a large fibroepithelial polyp occupied the entire left nasal cavity and extended into the nasopharynx. A gross total resection was performed. It appeared to be originating from the left sphenoethmoid recess near the skull base. The maxillary and ethmoid sinuses were not involved but the polyps obstructed the sphenoid sinus ostium. Additional polypoid tissue found the right sphenoethmoid recess was also grossly removed. Follow-up imaging study showed a large persistent mass is in the sphenoid sinuses, and she underwent a revision functional endoscopy sinus surgery. Intraoperatively, a residual NCMH was removed from the right sphenoethmoid recess, posterior septum and left sphenoid sinus. Microscopic tumor images are available in Figure 1. Multiple years following the last resection she continues to be well with no further recurrence of NCMH.

Figure 1. Pathology Images (case #60 in Table 2).



A: Hematoxylin and eosin (H & E) staining of NCMH with multiple cartilage islands (arrows) in polypoid nasal mucosa (10x magnification). B: H & E staining of NCMH with immature cartilage island (arrow) in paranasal sinus polypoid mucosa (20x magnification).

Discussion

The primary goal of this investigation was to determine if there were any differences in sinonasal symptoms or otorhinolaryngologic exam findings between *DICER1*-carriers and family controls; none were found. No NCMH were discovered during the patients' clinical evaluations at the NIH Clinical Center, although two cases of NCMH developed at 53 and 84 months after their clinic evaluation (including unremarkable endoscopies performed during their clinical evaluation). A prospective quantification of risk of NCMH in *DICER1*-carriers has not been published in the literature prior to this study although estimates of overall lifetime risk of neoplasm development in *DICER1*-carriers have been recently published [21].

As a rare tumor, a diagnosis of NCMH should prompt referral to a pediatric oncologist or geneticist for *DICER1* genetic testing. If a pathogenic germline *DICER1* variant is found, the patient should undergo lifelong surveillance [20] to detect, as early as possible, other *DICER1*-associated neoplasms. In addition, family members should undergo *DICER1* cascade genetic testing to detect other individuals, especially children, at risk. In individuals with negative germline *DICER1* testing, there should be consideration for NCMH *DICER1* sequencing for research purposes or to evaluate for potential mosaicism. In a *DICER1*-carrier, there should be a low threshold for referral for otorhinolaryngologic evaluation for chronic rhinorrhea, nasal congestion or recurrent sinusitis (especially unilateral), snoring, nasal masses, proptosis of the eye or nasomaxillary pain. While NCMH are histologically benign, they can be locally invasive into adjacent structures like the orbit and skull base. Early detection and removal can lead to improved outcome and decrease the likelihood of recurrence.

While there are proposed surveillance guidelines for *DICER1*-carriers [20], the rarity and benign nature of NCMH does not support routine imaged-based surveillance for this entity, however, detailed evaluation is needed for symptoms of sinonasal obstruction. In 63% of the cases, NCMH occurred in the ethmoid sinus, orbit or skull base. Tumors in these places could be missed with nasal endoscopy, especially in a small child or infant. With persistence of concerning symptoms, further evaluation may be required, which may include CT, MRI and/or even ultrasound in children less than 12 months looking for a mass, bony destruction or bony remodeling. Patients with PPB Type II or Type III routinely undergo a staging evaluation and surveillance that includes an MRI of the brain. In these cases, we would propose paying specific attention to the nasal cavity and sinuses to look for potential NCMH tumors at that time. A recent publication utilizing this same cohort of patients reported other neoplasms in *DICER1*-carrriers with NCMH. Over 50% of the patients with NCMH were diagnosed with PPB and the remainder with other classical *DICER1*-associated tumors [21].

Limitations of this study include recall bias by patients during completion of the review of symptoms screening prior to the otolaryngology visit. It is possible that other NCMH diagnoses were missued using a follow up quiestionnaire.

Conclusions

In summary, while no particular symptom is pathognomonic for NCMH, clinicians should have a lower threshold to obtain additional evaluation on *DICER1*-carriers with persistent nasal symptoms. Second, for patients in which NCMH is diagnosed, germline genetic testing for *DICER1* is essential for the patient and their family. If positive, surveillance imaging, especially in children and females, is indicated. Lastly, we report quantification of the risk of NCMH from a prospectively followed cohort.

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Authorship contribution

LV analayzed the data, performed statistical analysis, prepared the manuscript, tables and figures and coordinated for submision. AN collected the original clinical information and created a usable data file for review. LH is the coordinator for the clinical trial and is responsible for ensuring clinical documentation is maintained on the particpants, including consents, and was responsible for collecting the pathologic and radiologic imaging. AB oversaw the statistical analysis and provided instruction on determining person-years. AG collected and analyszed the genetic variants. AH and KS provided additional cases of NCMH from the PPB registry. MM reviewed all of the pathology of the tumor samples and provided the pathology imaging. HK saw each patient in the otolaryngology clinic and provided the clinical information reviewed for data collection. DS is the principle investigator on the protocol and oversaw LV during every step of data analysis and manuscript production. KS, HK and DS additionally provided mentorship and guidance during the manuscript prouction. All authors read and approved the final manuscript.

Conflict of interest

DRS provides contract clinical telegenetics services to Grenome Medical Inc. in accordance with relevant NCI ethics policies.

Ethics approval and consent to participate

This study was conducted under the IRB-approved protocol "*DICER1*-related Pleuropulmonary Blastoma Cancer Predisposition Syndrome: A Natural History Study" (NCI Protocol 11-C-0034; NCT-01247597). All subjects provided written informed consent. For patients less than 18 years of age, parents provided written consent. Patients older than 10 years but less than 18 also provided written assent.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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List of Abbreviations

NCMH – nasal chondromesenchymal hamartoma; PPB – pleuropulmonary blastoma; NCI – National Cancer Institute; NIH – National Institutes of Health; CT - computed topography; MRI – magnetic resonance imaging; ND – not documented; H & E - hematoxylin and eosin; M = male; F= female.

References

1. Hill DA, Ivanovich J, Priest JR, Gurnett CA, Dehner LP, Desruisseau D, et al. *DICER1* mutations in familial pleuropulmonary blastoma. Science. 2009;325(5943):965.
2. Doros L, Schultz KA, Stewart DR, Bauer AJ, Williams G, Rossi CT, et al. *DICER1*-Related Disorders. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews((R)). Seattle (WA)1993.
3. Stewart DR, Messinger Y, Williams GM, Yang JD, Field A, Schultz KAP, et al. Nasal chondromesenchymal hamartomas arise secondary to germline and somatic mutations of *DICER1* in the pleuropulmonary blastoma tumor predisposition disorder. Human Genetics. 2014;133(11):1443-50.
4. Golbin DA, Ektova AP, Demin MO, Lasunin N, Cherekaev VA. Nasal Chondromesenchymal Hamartoma with Skull Base and Orbital Involvement: Case Presentation. Cureus. 2018;10(6):e2892.
5. McDermott MB, Ponder TB, Dehner LP. Nasal chondromesenchymal hamartoma: an upper respiratory tract analogue of the chest wall mesenchymal hamartoma. Am J Surg Pathol. 1998;22(4):425-33.
6. Mason KA, Navaratnam A, Theodorakopoulou E, Chokkalingam PG. Nasal Chondromesenchymal Hamartoma (NCMH): a systematic review of the literature with a new case report. J Otolaryngol-Head N. 2015;44.
7. Martins D, Barroca H. Nasal chondromesenchymal hamartoma in a 22 days newborn baby: case report. Virchows Archiv. 2018;473:S148-S.
8. Sutter T, Becker C, Pfeiffer J. Nasal chondromesenchymal hamartoma: Case report. Laryngo-Rhino-Otologie. 2018;97:1.
9. Mirchia K, Naous R. Nasal Chondromesenchymal Hamartoma: Rare Case Report in an Elderly Patient and Brief Review of Literature. Case Reports in Pathology. 2018.
10. Karimnejad K, Rohde RL, Costa DJ. A Congenital Nasal Mass Causing Respiratory Distress. JAMA Otolaryngol Head Neck Surg. 2017;143(4):417-8.
11. Nakaya M, Yoshihara S, Yoshitomi A, Baba S. Endoscopic endonasal excision of nasal chondromesenchymal hamartoma with intracranial extension. Eur Ann Otorhinolaryngol Head Neck Dis. 2017;134(6):423-5.
12. Bueno MT, Martinez-Rios C, la Puente Gregorio A, Ahyad RA, Villani A, Druker H, et al. Pediatric imaging in *DICER1* syndrome. Pediatr Radiol. 2017;47(10):1292-301.
13. Unal A, Kum RO, Avci Y, Unal DT. Nasal chondromesenchymal hamartoma, a rare pediatric tumor: Case report. Turkish J Pediatr. 2016;58(2):208-11.
14. Avci H, Comoglu S, Ozturk E, Bilgic B, Kiyak OE. Nasal chondromesenchymal hamartoma: a rare nasal benign tumor. Kulak Burun Bogaz Ihtis Derg. 2016;26(5):300-3.
15. Macharia BN, Sisenda TM, Tabitha C, Rono BC. Nasal chondromesenchymal hamar-

toma in a nine year old female: Case report. East African Medical Journal. 2016;93.
16. Lee CH, Park YH, Kim JY, Bae JH. Nasal chondromesenchymal hamartoma causing sleep-disordered breathing in an infant. Int J Clin Exp Pathol. 2015;8(8):9643-6.
17. Schultz KA, Yang J, Doros L, Williams GM, Harris A, Stewart DR, et al. *DICER1*-pleuropulmonary blastoma familial tumor predisposition syndrome: a unique constellation of neoplastic conditions. Pathol Case Rev. 2014;19(2):90-100.
18. Nakano Y, Hasegawa D, Stewart DR, Schultz KAP, Harris AK, Hirato J, et al. Presacral malignant teratoid neoplasm in association with pathogenic *DICER1* variation. Mod Pathol. 2019.
19. Huryn LA, Turriff A, Harney LA, Carr AG, Chevez-Barrios P, Gombos DS, et al. *DICER1* Syndrome: Characterization of the Ocular Phenotype in a Family-Based Cohort Study. Ophthalmology. 2019;126(2):296-304.
20. Schultz KAP, Williams GM, Kamihara J, Stewart DR, Harris AK, Bauer AJ, et al. *DICER1* and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies. Clin Cancer Res. 2018;24(10):2251-61.
21. Stewart DR, Best AF, Williams GM, Harney LA, Carr AG, Harris AK, et al. Neoplasm Risk Among Individuals With a Pathogenic Germline Variant in *DICER1*. J Clin Oncol. 2019:JCO2018784678.

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SUPPLEMENTARY INFORMATION

Additional case summaries

Multiple *DICER1*-carriers had NCMH resected prior to enrollment into the study or after evaluation at the NIH. Two additional unpublished NCMH cases from the NCI study and Registry cohort are outlined below. The specific timeframes have been generalized to protect patient privacy.

Case 63 in Table 2

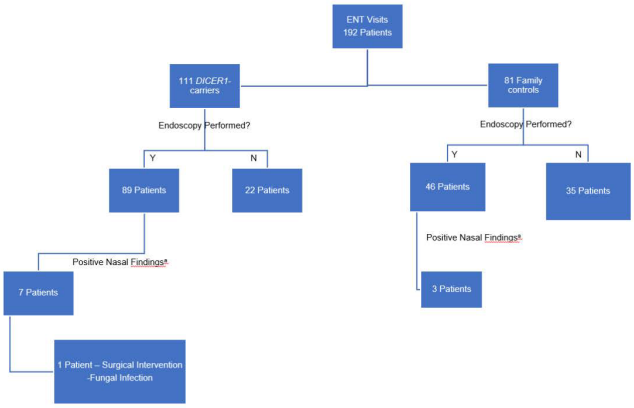
A female with multiple *DICER1* tumors is followed in the Field Cohort. She has not been formally evaluated as part of the Clinic Cohort to date. She has a *DICER1* frameshift variant c.4407_4410delTTCT (p.Ser1470Leufs). She developed her first tumor, a presacral primitive neuroectodermal tumor, as an infant and was treated with vincristine and cyclophosphamide and tandem autologous stem cell transplants (conditioning with etoposide, cyclophosphamide and carboplatin). During this time, she also was found to have a presacral malignant teratoid neoplasm of the pelvis which has been previously reported [18]. As a young child, she developed rhabdomyosarcoma of the vagina, treated with vincristine, dactinomycin, cyclophosphamide, irinotecan and 15 Gy of whole abdominal radiation with pelvic boost of 45 Gy. She developed the following tumors subsequently: thyroid carcinoma, NCMH and metachronous spindle cell/cystic nephroma of the right and left kidneys. Her NCMH was 2.4 x 1.3 x. 3.6 cm in the left side, extending into the left sphenoid, posterior right nasal cavity, inferiorly into the nasopharynx and attached to the skull base. A few years after her NCMH resection, she was experiencing intermittent epistaxis and felt as if she could feel something inside her nose. Nasal endoscopy showed a white lesion in the right nare confirmed by CT imaging (sFigure 2). Excision of the mass confirmed NCMH, located in the right nasal cavity, surrounding the middle turbinate and attached to the skull base. This mass was fully resected and determined to be NCMH.

Case 64 in Table 2

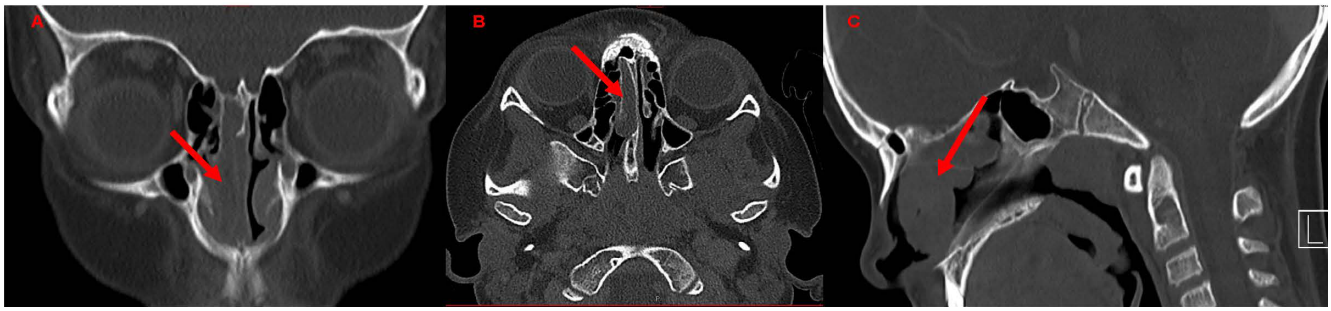
A female with *DICER1* c.1408G>T, p.E470* was seen at the NIH as a young child after her sister was diagnosed with Type II PPB. At that time, she had no concerning physical exam or endoscopy findings. Several years later she developed a left eye medulloepithelioma that required enucleation which has been previously reported[19]. Two years after that, she had a thyroidectomy for thyroid nodules with cytologic atypia. Brain MRIs the time of the medulloepithelioma diagnosis and during post-operative surveillance did not show any intranasal or sinus disease or concern for a mass. A few years later, the patient was evaluated for several months of chronic nasal congestion. Endoscopic evaluation showed a nasal mass which was resected. Pathology demonstrated areas of ossification within the nasal cartilage islands (sFigure 3) consistent with NCMH.

Supplementary Table 1. Frequency of sinonasal signs and symptoms in *DICER1*-carriers vs. family controls

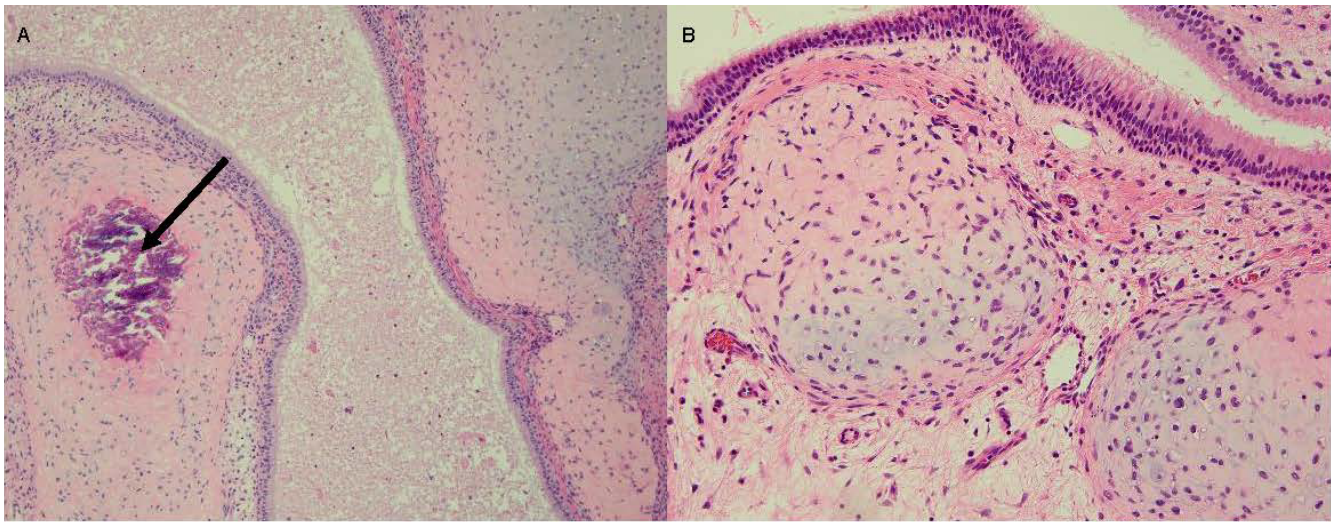
Symptom	*DICER1*-Carriers n=111 (%)	Family Controls n = 81 (%)	p-value
Congestion	29 (26%)	23 (28%)	0.77
Rhinorrhea	27 (24%)	17 (21%)	0.60
Epistaxis	14 (13%)	10 (12%)	1
Post-Nasal Drip	17 (15%)	17 (21%)	0.34
Sinus/Facial Pain	4 (4%)	7 (9%)	0.21
Cough	27 (24%)	10 (12%)	0.06
Sneezing	27 (24%)	8 (22%)	0.86
Sinusitis	20 (18%)	15 (19%)	1
Anosmia	4(4%)	0 (0%)	0.14
Barotrauma	6 (5%)	3 (4%)	1
Recurrent Acute Otitis Media	7 (6%)	6 (7%)	0.78



Supplementary Figure 1. Flow diagram describing nasal findings during nasal endoscopy in *DICER1*-carriers and family controls. a. Positive Nasal Findings = polyps, polypoid tissue, or yellow-colored rhinorrhea.



Supplementary Figure 2. Sinus CT - A: (coronal view) An opacified mass filling the entire right nasal cavity and extending up to the fovea ethmoidalis and cribriform. The crista galli of the cribriform deviated to the left side. B: (axial view) A nasal expansile mass filling the right medial nasal cavity. C: (sagittal view) Right nasal mass extending up to the fovea ethmoidalis (case #64 in Table 2).



Supplementary Figure 3. Pathology Images (case #64 in Table 2). A: H & E staining of NCMH with focal ossification (arrow) within cartilage island of polypoid nasal mucosa (10x magnification). B: H & E staining of NCMH with cartilage islands in paranasal sinus polypoid mucosa (20x magnification).

Supplementary Table 2. Review of published nasal mesenchymal hamartoma cases from 2015 through February 2019.

Case No.	Age at Presentation/ Gender	Side & Size	Symptoms	Site	Co-morbidity	Investigations	Treatment/ Follow Up
58 [3]	22 days/ND[a]	ND	1. Nasal obstruction 2. Tachypnea 3. Peripheral cyanosis	Nasal cavity	ND	MRI	Excision/ND
57[4]	8 months/F	Right	1. Feeding Difficulties 2. Nasal Obstruction	Nasal cavity Maxillary Sinus Ethmoid labyrinth Orbit Skull Base	ND	CT, MRI	Partial Excision/ 2nd Resection at 23 months
56[5]	24 months/M	Right	1. Snoring 2. Nasal mass	Nasal Cavity Maxillary sinus Ethmoid Sinus	ND	CT, MRI	Excision/No recurrence at 16 months postoperatively
55[6]	70 years/F	Right (2.5 x 2.1cm)	1. Chronic maxillary 2. sinusitis 3. Slow growing mass	Nasal cavity Maxillary Sinus	ND	CT	Excision/ND
54[7]	12 days/M	Left (2.0 x 1.6cm)	1. Nasal obstruction 2. Nasal congestion 3. Poor feeding	Nasal cavity Cribriform plate	ND	CT	Excision/ND
53[8]	3 years/M	Right (3.5 x 5.3 x 4.5 cm)	1. Excessive lacrimation 2. Proptosis 3. Disturbed eye 4. movement	Nasal cavity Ethmoid sinus Orbit Anterior cranial fossa	ND	CT, MRI	Excision/No recurrence at 6 years old
52[9]	2.58 years/F[b]	ND	1. ND	ND	PPB (after NCMH)	CT	ND/No recurrence at 19 months post
51[10]	13 years/F	Left (3.3 x 6.1 cm)	1. Nasal obstruction	Nasal cavity Frontal sinus Sphenoid sinus	ND	CT	Excision/No recurrence at 1 year postoperatively
50[11]	5 years/M	Left	1. Nasal obstruction 2. Recurrent sinusitis	Nasal cavity Olfactory cleft Anterior skull base	Rhabdomyosarcoma (neck)	MRI	Excision/No recurrence at 4 months postoperatively
49[12]	9 years/F	Left (~4cm)	1. Nasal Mass 2. Difficulty breathing 3. Pain	Nasal Cavity Ethmoid Sinus Maxillary Sinus	ND	CT, Endoscopy	Excision/Died from complications of surgery
48[13]	10 months/M	Right	1. Sleep-disordered 2. breathing 3. Nasal congestion 4. Mouth-breathing 5. Snoring 6. Periodic apnea	Nasal cavity Cribriform plate	ND	CT, MRI	Excision/No recurrence at 18 months postoperatively
47[14]	13 years/M[b]	Bilateral	1. Nasal congestion	Sinonasal	Peritoneal PPB PPB II SLCT Thyroid NOS	Endoscopy	Excision/No recurrence at 18 years old

ND - Not Documented; PPB – Pleuropulmonary Blastoma; CT - Computed Topography scan; MRI – Magnetic Resonance Imaging; SLCT – Sertoli Leydig cell tumor. [a] Had *DICER1* testing that was negative. [b] *DICER1* testing positive; M = Male; F = female.

Supplementary References

1. Nakano Y, Hasegawa D, Stewart DR, Schultz KAP, Harris AK, Hirato J, et al. Presacral malignant teratoid neoplasm in association with pathogenic DICER1 variation. Mod Pathol. 2019.
2. Huryn LA, Turriff A, Harney LA, Carr AG, Chevez-Barrios P, Gombos DS, et al. DICER1 Syndrome: Characterization of the Ocular Phenotype in a Family-Based Cohort Study. Ophthalmology. 2019;126(2):296-304.
3. Martins D, Barroca H. Nasal chondromesenchymal hamartoma in a 22 days newborn baby: case report. Virchows Archiv. 2018;473:S148-S.
4. Golbin DA, Ektova AP, Demin MO, Lasunin N, Cherekaev VA. Nasal Chondromesenchymal Hamartoma with Skull Base and Orbital Involvement: Case Presentation. Cureus. 2018;10(6):e2892.
5. Sutter T.; Becker C.; Pfeiffer J. Nasal chondromesenchymal hamartoma: Case report. Laryngo-Rhino-Otologie. 2018;97:1.
6. Mirchia K, Naous R. Nasal Chondromesenchymal Hamartoma: Rare Case Report in an Elderly Patient and Brief Review of Literature. Case Reports in Pathology. 2018.
7. Karimnejad K, Rohde RL, Costa DJ. A Congenital Nasal Mass Causing Respiratory Distress. JAMA Otolaryngol Head Neck Surg. 2017;143(4):417-8.
8. Nakaya M, Yoshihara S, Yoshitomi A, Baba S. Endoscopic endonasal excision of nasal chondromesenchymal hamartoma with intracranial extension. Eur Ann Otorhinolaryngol Head Neck Dis. 2017;134(6):423-5.
9. Bueno MT, Martinez-Rios C, la Puente Gregorio A, Ahyad RA, Villani A, Druker H, et al. Pediatric imaging in DICER1 syndrome. Pediatr Radiol. 2017;47(10):1292-301.
10. Unal A, Kum RO, Avci Y, Unal DT. Nasal chondromesenchymal hamartoma, a rare pediatric tumor: Case report. Turkish J Pediatr. 2016;58(2):208-11.
11. Avci H, Comoglu S, Ozturk E, Bilgic B, Kiyak OE. Nasal chondromesenchymal hamartoma: a rare nasal benign tumor. Kulak Burun Bogaz Ihtis Derg. 2016;26(5):300-3.
12. Macharia BN, Sisenda TM, Tabitha C, Rono BC. Nasal chondromesenchymal hamartoma in a nine year old female: Case report. East African Medical Journal. 2016;93.
13. Lee CH, Park YH, Kim JY, Bae JH. Nasal chondromesenchymal hamartoma causing sleep-disordered breathing in an infant. Int J Clin Exp Pathol. 2015;8(8):9643-6.
14. Schultz KA, Yang J, Doros L, Williams GM, Harris A, Stewart DR, et al. DICER1-pleuropulmonary blastoma familial tumor predisposition syndrome: a unique constellation of neoplastic conditions. Pathol Case Rev. 2014;19(2):90-100.