Nasal chondromesenchymal hamartomas in a cohort with pathogenic germline variation in \textit{DICER1}*

Lauren M. Vasta$^{1,2}$, Alison Nichols$^1$, Laura A. Harney$^3$, Ana F. Best$^4$, Ann G. Carr$^3$, Anne K. Harris$^5$, Markku Miettinen$^6$, Kris Ann P. Schultz$^{5,7}$, Hung Jeffrey Kim$^{8,9}$,$^\#$, Douglas R. Stewart$^{1,\dagger}$

$^1$Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Rockville, MD, USA
$^2$National Capital Consortium, Walter Reed National Military Medical Center, Bethesda, MD, USA
$^3$Westat, Inc, Rockville, MD, USA
$^4$Biostatistics Branch, Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, NIH, Rockville, MD, USA
$^5$International Pleuropulmonary Blastoma/DICER Registry, Minneapolis, MN, USA
$^6$Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA
$^7$Cancer and Blood Disorders Program, Children’s Minnesota, Minneapolis, MN, USA
$^8$Office of Clinical Director, National Institute on Deafness and Other Communication Disorders, NIH, Bethesda, MD
$^9$Department of Otolaryngology-HNS, Georgetown University Medical Center, Washington, DC, USA

$^\#$ These authors contributed equally

\textbf{Abstract}

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

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both the NCI \textit{DICER1} study and the International Pleuropulmonary Blastoma/DICER Registry were queried for unpublished cases of nasal chondromesenchymal hamartomas.

\textbf{Results}: There were no clinical differences in sinonasal symptomatology between \textit{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 \textit{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 \textit{DICER1}-associated tumor and 24\% of the NCCH were found in the ethmoid sinus, the most commonly involved paranasal sinus.

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

\textbf{Key words}: \textit{DICER1}, nasal chondromesenchymal hamartoma, microRNA, pleuropulmonary blastoma

\textit{Trial registration}: \textit{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.

Rhinology Online, Vol 3: 15 - 24, 2020
http://doi.org/10.4193/RHINOL/202007

*Received for publication: January 23, 2020
Accepted: March 7, 2020
Published: April 13, 2020
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 chondromesenchymal 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 (3). Interestingly, this initial report identified one child with an NCMH and prior history of pleuropulmonary blastoma (1).

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 otolaryngology 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) (6, 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-
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 (Figure 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 DICER1-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 1. Demographics of 192 DICER1-carriers and control individuals.

| Parameter       | DICER1-Carriers n=111 (%) | Family Controls n=81 (%) |
|-----------------|----------------------------|--------------------------|
| Age < 18 yearsa | 50 (45%)                   | 21 (26%)                 |
| Age ≥ 18 yearsa | 61 (55%)                   | 60 (74%)                 |
| Malea           | 52 (47%)                   | 45 (55%)                 |
| Femaleb         | 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).

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 | Investigationsa,b | Follow-up |
|----------|---------------------------|-------------|----------|------|--------------|------------------|-----------|
| 64       | 10 years/F                | Right       | 1. Nasal Congestion | 1. Nasal Cavity | Medulloepithelioma, Thyroid Nodules19 | 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 teratoma19 | 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.
A female child with germline DICER1 c.2040+1G>T mutation was diagnosed as a young child with PPC Type II. She underwent left lower lobectomy and 43 weeks of adjuvant chemotherapy with doxorubicin, vincristine, cyclophosphamide, ifosfamide, topotecan and carboplatin. After treatment, she developed local recurrence and underwent resection followed by 44 Gy of radiation. She has had no further nasal symptoms, regrowth of the mass or additional concern for PPB recurrence. She is currently following surveillance recommendations for having DICER1-associated disease.

Case 59 in Table 2
A female child with germline DICER1 c.2040+1G>T mutation was diagnosed at seven years of age and underwent 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 currently follows published surveillance recommendations.

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 with published (Supplementary Table 2) and unpublished (Table 2) 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 to 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 50 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, dactinomyacin 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 MR 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 sphenethmoid 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 sphenethmoid 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. Intraperatively, a residual NCMH was removed from the right sphenethmoid 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.

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 and 43 weeks of adjuvant 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 included 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.

Nasal tumors in DICER1-carriers
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 clinical 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-carriers 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 missed using a follow up questionnaire.

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.
Nasal tumors in DICER1-carriers

Acknowledgement
The content of this publication does not necessarily reflect the official views or policies of the Department of Health and Human Services, Department of the Army/Navy/Air Force, Department of Defense, nor does mention of trade names, commercial products or organizations imply endorsement by the U.S. Government.

Authorship contribution
LV analyzed the data, performed statistical analysis, prepared the manuscript, tables and figures and coordinated for submission. 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 participants, 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 analyzed 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 production. All authors read and approved the final manuscript.

Conflict of interest
DRS provides contract clinical telegenetics services to Gnome 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.

Funding
This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute, Bethesda, MD. The International PPB/DICER1 Registry is supported by Pine Tree Apple Classic Fund and Children’s Minnesota Foundation.

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(5):1485-8.
8. Sutter T, Becker C, Pfeiffer J. Nasal chondromesenchymal hamartoma: Case report. Laryngo-Rhino-Otolologie. 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, Kurn RÖ, 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, Oztkur 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 hamartoma with intracranial extension. Eur Ann Otorhinolaryngol Head Neck Dis. 2017;134(6):423-5.
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 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.
Nasal tumors in DICER1-carriers

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<sup>(5)</sup> | 22 days/ND<sup>a</sup> | ND | 1. Nasal obstruction 2. Tachypnea 3. Peripheral cyanosis | Nasal cavity | ND | MRI | Excision/ND |
| 57<sup>(6)</sup> | 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<sup>(7)</sup> | 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<sup>(8)</sup> | 70 years/F (2.5 x 2.1 cm) | Right | 1. Chronic maxillary sinusitis 2. Slow growing mass | Nasal cavity Maxillary Sinus | ND | CT | Excision/ND |
| 54<sup>(9)</sup> | 12 days/M (2.0 x 1.6 cm) | Left | 1. Nasal obstruction 2. Nasal congestion 3. Poor feeding | Nasal cavity | ND | CT | Excision/ND |
| 53<sup>(10)</sup> | 3 years/M (3.5 x 5.3 x 4.5 cm) | Right | 1. Excessive lacrimation 2. Proptosis 3. Disturbed eye movement | Nasal cavity Ethmoid sinus Orbit Anterior cranial fossa | ND | CT, MRI | Excision/No recurrence at 6 years old |
| 52<sup>(11)</sup> | 2.58 years/F<sup>b</sup> | ND | 1. ND | ND | PPB (after NCMH) | CT | ND/No recurrence at 19 months postoperatively |
| 51<sup>(12)</sup> | 13 years/F (3.3 x 6.1 cm) | Left | 1. Nasal obstruction | Nasal cavity Frontal sinus Sphenoid sinus | ND | CT | Excision/No recurrence at 1 year postoperatively |
| 50<sup>(13)</sup> | 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<sup>(14)</sup> | 9 years/F (~4cm) | Left | 1. Nasal Mass 2. Difficulty breathing 3. Pain | Nasal Cavity Ethmoid Sinus Maxillary Sinus | ND | CT, Endoscopy | Excision/Died from complications of surgery |
| 48<sup>(15)</sup> | 10 months/M | Right | 1. Sleep-disordered breathing 2. Nasal congestion 3. Mouth-breathing 4. Snoring 5. Periodic apnea | Nasal cavity | ND | CT, MRI | Excision/No recurrence at 18 months postoperatively |
| 47<sup>(16)</sup> | 13 years/M<sup>b</sup> | 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. * Had DICER1 testing that was negative. * 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;475:514-5.

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. Mirchka 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, Biligic B, Kiyak OE. Nasal chondromesenchymal hamartoma: a rare nasal benign tumor. Kulak Burun Bogaz Ihtis Derg. 2016;26(5):300-3.

12. Macharia BN, Sienda 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.

ISSN: 2589-5613 / ©2020 The Author(s). This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/