NIH NATIONAL CANCER INSTITUTE

Pleuropulmonary Blastoma

DICER1 STUDY *Newsletter*

Fall 2022

Division of Cancer Epidemiology and Genetics • Clinical Genetics Branch

IN THIS ISSUE

A NOTE FROM THE STUDY TEAM

We are pleased to share the first newsletter from the *DICER1*-Related Pleuropulmonary Blastoma (PPB) Syndrome Study! In this inaugural issue, we discuss highlights of our research, provide study updates, introduce our research team, and more.

As we celebrate the 10th anniversary of the launch of the *DICER1* study, we want to share our appreciation for you, our patients and families. Your participation in the International PPB/*DICER1* Registry has made it possible to improve the care of children and families living with the effects of disease-causing genetic alterations in the *DICER1* gene. Your ongoing collaboration matters and we are grateful to you for it!

We hope you enjoy this issue. Feel free to let us know what you think and share any feedback on what you'd like to see in the future!

Contact: Laura Harney at laura.harney@nih.gov

GOALS OF THE *DICER1* STUDY

- Determine the frequency of *DICER1* germline disease-causing variants in the general population as well as among affected individuals
- Identify the kinds of tumors and risks associated with those variants
- Develop *DICER1* evidence-based cancer screening and clinical management guidelines
- Discover why some variant carriers develop cancer while others remain healthy
- Identify medical conditions that arise in individuals with a *DICER1* variant as they get older.

ACCOMPLISHMENTS

We are celebrating our 10th anniversary and looking forward to the continued successes of this study. Our work has already had a meaningful effect on the care of children and adults with a disease-causing variant in *DICER1*. The published research studies from the study have:

- Proposed guidelines for health and cancer screening protocols for individuals with a *DICER1* disease-causing variant
  - See proposed screening guidelines at the link provided, specifically Table 2: https://go.usa.gov/xuvdJ
- Identified novel tumor types associated with *DICER1*
- Identified non-tumor features (such as a larger head circumference, certain types of kidney abnormalities, and others) in people with a *DICER1* disease-causing variant
- Provided estimates of cancer risk for males and females with a *DICER1* disease-causing variant across the lifespan
- Provided estimates of the risk of thyroid disease for males and females with a *DICER1* disease-causing variant across the lifespan
- Informed a large collaborative effort to refine the rules to define exactly what a *DICER1* disease-causing variant is and to ensure variants are interpreted the same way across all labs
- Shown that *DICER1* disease-causing variants are more common than expected in the population

RECRUITMENT

We have enrolled more than 712 patients from 113 families since the study opened in November 2010.

Your time and commitment have enabled us to establish a group of individuals and families with *DICER1*-related conditions, including pleuropulmonary blastoma (PPB) cystic nephroma and Sertoli-Leydig cell tumors. This has allowed us to learn more about these tumors and the importance of screening and early detection for people with a *DICER1* variant. Our progress is a direct reflection of the participation of families like yours.

Please stay in touch with our study team by completing the periodic follow-up questionnaires you may receive and update us with any new health concerns by contacting Laura Harney at laura.harney@nih.gov.

STUDY TEAM MEMBERS

Principal Investigator

Douglas Stewart, M.D., an internist and medical geneticist, is the principal investigator of the *DICER1* study. Dr. Stewart has a special interest in familial cancer syndromes.

Clinical Team

Margarita Aryavand, M.S.N., C.F.N.P., nurse practitioner and Captain, U.S. Public Health Service, assesses the genetic causes and clinical features of RASopathies and examines the role of genetic and environmental factors in the etiology of cancer and related conditions.

Mary Lou McMaster, M.D., senior clinical specialist and Captain, U.S. Public Health Service, characterizes the clinical spectrum of *DICER1* families and explores genotype-phenotype correlations.

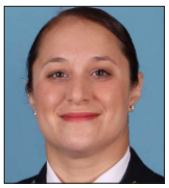
Scientific Team

Ana Best, Ph.D., a mathematical statistician in NCI's Division of Cancer Treatment and Diagnosis, has played a key role in developing estimates of cancer risk in people with a disease-causing *DICER1* variant.

Jung Kim, Ph.D., staff scientist, studies the population genetics and phenotype of *DICER1* and the associated miRNA processing genes; she also analyzes somatic genomic data of *DICER1*-associated malignancies.

Jessica Hatton, M.S., C.G.C., a genetic counselor who works to interpret the clinical significance of different *DICER1* genetic variants.

Special Volunteer



Lauren Vasta, M.D., Major, U.S. Army and Chief of Pediatric Hematology and Oncology at Tripler Army Medical Center, serves the study as a Clinical Fellow in a special volunteer status. Her current *DICER1* interests involve examining the phenotype of *DICER1*-carriers and examining associated underlying genetics.

Scientific Support

Cecilia Higgs, M.H.S. program manager, leads the regulatory matters of the study and manages the study files, including the protocol, consent documents, and submissions to the Institutional Review Board.

Study Support

Laura Harney, R.N., B.S.N., is a registered nurse who supports cancer genetics research.

Ann Carr, M.S., C.G.C., is a genetic counselor with many years of experience in both cancer and pediatric genetics.

Stephanie Steinbart, R.N., M.P.H., is a research nurse who serves as the study referral nurse.

Neve Brennan, B.A. is a research assistant on the *DICER1* study.

Collaborators through the *DICER1* Registry

The *DICER1* study has been at the forefront of an exciting interdisciplinary collaboration, leading to new discoveries and insights in the causes and importance of early interventions for *DICER1*-related disorders. The NCI team and our collaborators through the International PPB/*DICER1* registry meet monthly to discuss new findings and patient study updates. Our collaboration extends across the country and includes the following people:

Kris Ann Schultz, M.D., is a pediatric oncologist and Scientific Director for Cancer and Blood Disorders at Children's Minnesota with expertise in the care of individuals with PPB, Sertoli-Leydig cell tumors (a rare form of ovarian cancer), and other *DICER1*-related tumors. She serves as Principal Investigator for the International PPB/*DICER1* and International Ovarian and Testicular Stromal Tumor Registries.

D. Ashley Hill, M.D., is a pediatric and molecular pathologist who led the family study that identified germline *DICER1* variants causing PPB and related tumors. She is a member of the International PPB/*DICER1* Registry and currently splits time with the Chilldren's National Hospital and her company, ResourcePath LLC.

Yoav Messinger, M.D., is a pediatric oncologist at Children's Minnesota with many years of experience treating children with PPB.

Louis "Pepper" Dehner, M.D., is a world-renowned pathologist at Washington University in St. Louis and was the first to characterize PPB in 1988.

Anne Harris, M.P.H., C.C.R.P., is a Clinical Research Specialist with the International PPB/*DICER1* Registry and International Ovarian and Testicular Stromal Tumor Registry.

Please visit the NCI PPB website
https://ppb.cancer.gov/
for full biographies and to find out more about the key staff members and their roles in the study.

UPDATES, COLLABORATIONS, AND NEW PROTOCOL DEVELOPMENTS

DICER1 and miRNA-Processing Gene Variant Curation Expert Panel for Clinical Genome Resource

Genetic variants in the *DICER1* gene are not always harmful and may not increase the risk of developing tumors like PPB. Some variants are perfectly normal and are simply part of what make a person's DNA unique. The ability to tell the difference accurately and consistently between harmful and normal variants (pathogenic and benign, respectively) detected by genetic testing is very important for figuring out who might need screening for *DICER1* syndrome.

To help with this process, Dr. Stewart has joined with the Clinical Genome Resource (ClinGen) to start and co-chair a variant curation expert panel (VCEP) for the *DICER1* gene. The VCEP is creating a rule system to determine whether variants are pathogenic or benign and hopefully to lessen the number of genetic test results that fall in the "uncertain" gray zone between the two categories. This effort will help more patients get accurate information about the meaning of their *DICER1* genetic test results. Ann Carr, Dr. Schultz, Dr. Hill and Dr. Kim have also participated in this effort by serving as experts on the VCEP. Jessica Hatton and Cecilia Higgs serve as coordinators.

Sequencing Work on Testicular Stromal Tumor

We conducted a recent study to examine the association, if any, between *DICER1* variants and testicular germ cell tumors, the most common type of testicular tumor. While we found no association, two individuals with pathogenic *DICER1* germline variants were identified as having a testicular stromal tumor (TST), a rare form of testicular tumor. One of the TSTs harbored a somatic *DICER1* hotspot variant, evidence of a possible association. Given these findings, we seek to explore the relationship between *DICER1* germline variation and TST development.

To do this, we are sequencing up to 200 TSTs to determine what proportion of these tumors harbor a *DICER1* variant. Results from this study could determine if TSTs are part of the *DICER1* phenotype and improve surveillance and screening recommendations for individuals and families with a germline *DICER1* variant.

RECENT PRESENTATIONS AND PAPERS

Presentations

New approaches to risk outcomes and phenotype in the *DICER1* syndrome
Grand Rounds, Moffitt Cancer Center, Tampa, FL, 2019.

Update on the NCI natural history study on *DICER1* syndrome
DICER1 Symposium, New Orleans, LA, 2019.

A "Genome First" Approach to Characterizing *DICER1* Pathogenic Variation Prevalence, Penetrance and Phenotype In 92,296 Individuals
Annual Meeting of the American College of Medical Genetics, San Antonio, Texas, 2020.

***DICER1* syndrome: An archetypal monogenic tumor-predisposition disorder**
PDQ Cancer Genetics Editorial Board, Rockville, MD, 2020.

New developments in *DICER1* syndrome for Hematology/Oncology Grand Rounds
Robert H. Lurie Comprehensive Cancer Center of Northwestern University and the Feinberg School of Medicine, Chicago, Illinois, January 2021.

Update on *DICER1* syndrome for the iCARE Case Conference
Vanderbilt Ingram Cancer Center, Nashville, Tennessee, February 2021.

The end of *DICER1*: a rare-disease public-health strategy to eliminate a childhood tumor-predisposition disorder
Intramural Scientific Investigators Retreat, National Cancer Institute, Gaithersburg, Maryland, March 2021.

A genome-first public health strategy to understand *DICER1*-related tumor-predisposition
DICER1 Symposium, International *DICER1*/PPB Registry, Children's Minnesota, May 2021.

Publications

Schultz KAP, Stewart DR, Kamihara J, et al. "***DICER1* Tumor Predisposition**." In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. 2014

Stewart DR, Messinger Y, Williams GM, et al. "**Nasal chondromesenchymal hamartomas arise secondary to germline and somatic mutations of *DICER1* in the pleuropulmonary blastoma tumor predisposition disorder**." *Hum Genet*. 2014

Brenneman M, Field A, Yang J, et al. "**Temporal order of RNase IIIb and loss-of-function mutations during development determines phenotype in pleuropulmonary blastoma / *DICER1* syndrome: a unique variant of the two-hit tumor suppression model.**" *F1000Res*. 2015

Messinger YH, Stewart DR, Priest JR, et al. "**Pleuropulmonary blastoma: a report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry**." *Cancer*. 2015

Khan NE, Bauer AJ, Doros L, et al. "**Macrocephaly associated with the *DICER1* syndrome**." *Genet Med*. 2017

Khan NE, Bauer AJ, Schultz KAP, et al. "**Quantification of Thyroid Cancer and Multinodular Goiter Risk in the *DICER1* Syndrome: A Family-Based Cohort Study**." *J Clin Endocrinol Metab*. 2017

Kim J, Field A, Schultz KAP, Hill DA, Stewart DR. "**The prevalence of *DICER1* pathogenic variation in population databases**." *Int J Cancer*. 2017

Schultz KAP, Harris AK, Finch M, et al. "***DICER1*-related Sertoli-Leydig cell tumor and gynandroblastoma: Clinical and genetic findings from the International Ovarian and Testicular Stromal Tumor Registry**." *Gynecol Oncol*. 2017

Khan NE, Ling A, Raske ME, et al. "**Structural renal abnormalities in the *DICER1* syndrome: a family-based cohort study.**" *Pediatr Nephrol*. 2018

Schultz KAP, Williams GM, Kamihara J, et al. "***DICER1* and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies.**" *Clin Cancer Res*. 2018

Huryn LA, Turriff A, Harney LA, et al. "***DICER1* Syndrome: Characterization of the Ocular Phenotype in a Family-Based Cohort Study**." *Ophthalmology*. 2019

Choi S, Lee JS, Bassim CW, et al. "**Dental abnormalities in individuals with pathogenic germline variation in *DICER1*.**" *Am J Med Genet A*. 2019

Kim J, Schultz KAP, Hill DA, Stewart DR. "**The prevalence of germline *DICER1* pathogenic variation in cancer populations.**" *Mol Genet Genomic Med*. 2019

Stewart DR, Best AF, Williams GM, et al. "**Neoplasm Risk Among Individuals With a Pathogenic Germline Variant in *DICER1*.**" *J Clin Oncol*. 2019

Merideth MA, Harney LA, Vyas N, et al. "**Gynecologic and reproductive health in patients with pathogenic germline variants in *DICER1***." *Gynecol Oncol*. 2020

Schultz KAP, Nelson A, Harris AK, et al. "**Pleuropulmonary blastoma-like peritoneal sarcoma: a newly described malignancy associated with biallelic *DICER1* pathogenic variation**." *Mod Pathol*. 2020

Vasta LM, Nichols A, Harney LA, et al. "**Nasal chondromesenchymal hamartomas in a cohort with pathogenic germline variation in *DICER1***." *Rhinol Online*. 2020

Vasta LM, McMaster ML, Harney LA, et al. "**Lack of pathogenic germline *DICER1* variants in males with testicular germ-cell tumors.**" *Cancer Genet*. 2020

Vasta LM, Khan NE, Higgs CP, et al. "**Hematologic indices in individuals with pathogenic germline *DICER1* variants**." *Blood Adv*. 2021

Mirshahi UL, Kim J, Best AF, et al. "**A Genome-First Approach to Characterize *DICER1* Pathogenic Variant Prevalence, Penetrance, and Phenotype.**" *JAMA Netw Open*. 2021;4(2):e210112. Published 2021

Venger K, Elbracht M, Carlens J, et al. "**Unusual phenotypes in patients with a pathogenic germline variant in *DICER1***". *Fam Cancer*. 2021

Golmard L, Vasta LM, Duflos V, et al. "**Testicular Sertoli cell tumour and potentially testicular Leydig cell tumour are features of *DICER1* syndrome**." *J Med Genet*. 2022

González IA, Stewart DR, Schultz KAP, Field AP, Hill DA, Dehner LP. "***DICER1* tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma**." *Mod Pathol*. 2022

Thank you for participating in the *DICER1*-Related PPB Syndrome Study! The strength of our study is in our participants.