資料9. PTEN, DICER1, FH and their Associated Tumor Susceptibility Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhoodのレビューワーク

小児期に発症する遺伝性腫瘍に対する
がんゲノム医療実装のための研究班

DICER1 syndrome

CCR Pediatric Oncology Seriesのレビューワーク ＋α

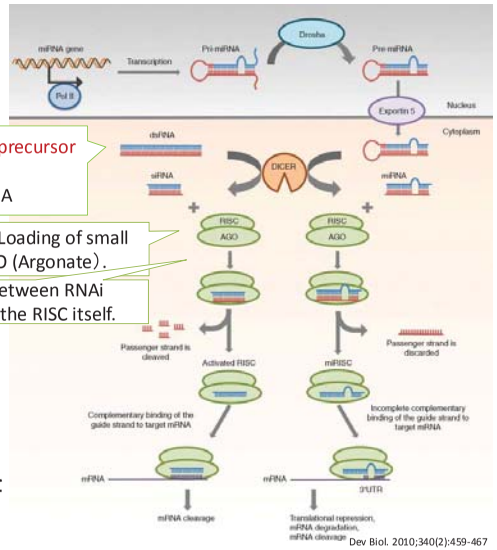
国立がん研究センター研究所 中野嘉子
東京大学 小児科 滝田順子

第三回班会議 2018/02/24

目次

DICER1とは？ その働き

- DICER1はriobonuclease として small RNAのprecursorを切断する。
  dsRNA⇒siRNA,
  miRNA precursor⇒miRNA



Processing of small RNA precursor
dsRNA⇒siRNA
Precursor miRNA⇒miRNA

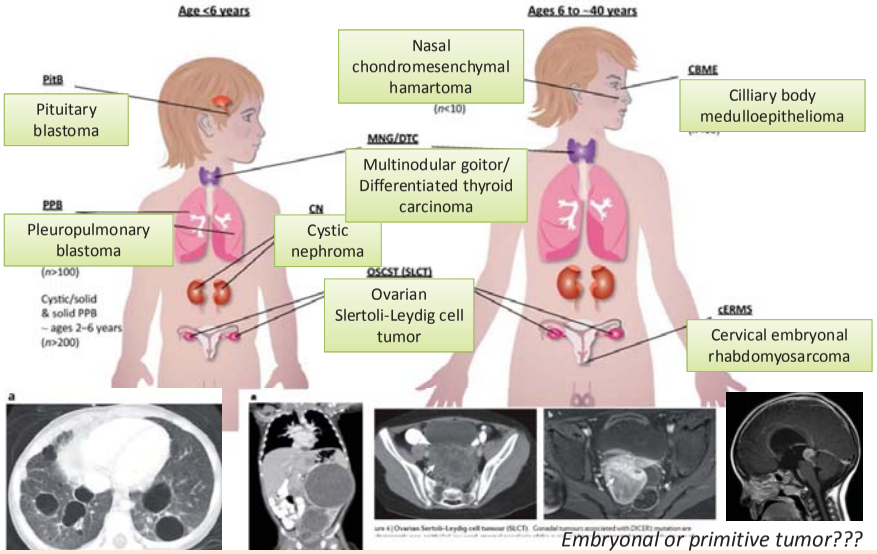
RISC loading；Loading of small RNA onto AGO (Argonate).

Interactions between RNAi cofactors and the RISC itself.

- DICER1は肺、皮膚、心臓、神経系など様々な発生において重要な役割を担う。
- 最近では、small RNAだけでなくmRNAにも結合しその安定性などを制御することも示唆されている。

Dev Biol. 2010;340(2):459-467
Nucleic Acids;2015: 4, e252
Cell. 2014;20(159):1153-1167

DICER1 syndrome



Embryonal or primitive tumor???

DICER1 Syndromeには様々な良性、悪性腫瘍が含まれる。

1996年： PPB が CPSである可能性を示唆した最初の報告

Pleuropulmonary blastoma: A marker for familial disease

John R. Priest, MD, Jan Watterson, BA, Louise Strong, MD, Vicki Huff, PhD, William G. Woods, MD, Rebecca L. Byrd, MD, Stephen H. Friend, MD, Irene Newsham, PhD, Michael D. Amylon, MD, Alberto Pappo, MD, Donald H. Mahoney, MD, Claire Langston, MD, Ruth Heyn, MD, Gloria Kohut, MD, David R. Freyer, DO, Bruce Bostrom, MD, Mary S. Richardson, MD, Julio Barredo, MD, and Louis P. Dehner, MD

From the Department of Hematology/Oncology, Children's Health Care, St. Paul, Minnesota; University of Texas M. D. Anderson Cancer Center, Houston, Texas; University of Minnesota Hospital, Minneapolis, Minnesota; Children's Hospital of the King's Daughters, Norfolk, Virginia; Fred Hutchinson Cancer Research Center, Seattle, Washington; University of California-San Diego, La Jolla, California; Lucile Salter Packard Children's Hospital at Stanford, Palo Alto, California; St. Jude Children's Research Hospital, Memphis, Tennessee; Texas Children's Hospital, Houston, Texas; University of Michigan Hospitals, Ann Arbor, Michigan; DeVos Children's Hospital at Butterworth, Grand Rapids, Michigan; Medical University of South Carolina, Charleston, South Carolina; and Barnes Hospital, St. Louis, Missouri

Objective: To catalog and evaluate patterns of disease in families of children with pleuropulmonary blastoma (PPB).
Methods: Data have been collected since 1988 on 45 children with PPB and their families. All pathologic materials were centrally reviewed. Preliminary molecular genetic analyses were performed when possible.
Results: In 12 of 45 patients, an association was found between PPB and other dysplasias, neoplasias, or malignancies in the patients with or in their young relatives. The diseases found to be associated with PPB include other cases of PPB, pulmonary cysts, cystic nephromas, sarcomas, medulloblastomas, thyroid dysplasias and neoplasias, malignant germ cell tumors, Hodgkin disease, leukemia, and Langerhans cell histiocytosis. Abnormalities of the p53 tumor suppressor gene, Wilms tumor suppressor gene (WT1), and the putative second genetic locus for Wilms tumor (WT2) were not found in preliminary investigations.
Conclusions: The occurrence of PPB appears to herald a constitutional and heritable predisposition to dysplastic or neoplastic disease in approximately 25% of cases. All patients with PPB and their families should be investigated carefully. Further research of this new family cancer syndrome may provide insight into the genetic basis of these diseases. (J Pediatr 1996;128:220-4)

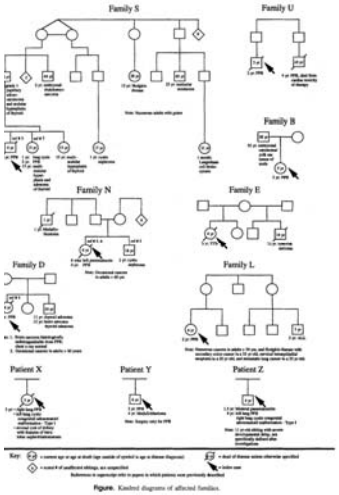


Figure. Kindred diagrams of affected families.

2001年：DICER1 がRNA iに関連するnucleaseとして同定された

Nature. 2001;18(409):363-6.

Role for a bidentate ribonuclease in the initiation step of RNA interference

Emily Bernstein*†, Amy A. Caudy*‡, Scott M. Hammond*§ & Gregory J. Hannon*

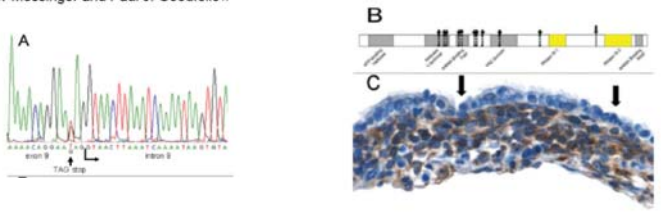
* Cold Spring Harbor Laboratory, and ‡Watson School of Biological Sciences, 1 Bungtown Road, Cold Spring Harbor, New York 11724, USA
† Graduate Program in Genetics, State University of New York at Stony Brook, Stony Brook, New York, 11794, USA
§ Genetica, 1 Kendall Square, Building 600, Cambridge, Massachusetts 01239, USA

2009年：familial PPB の原因が*DICER1* 変異である

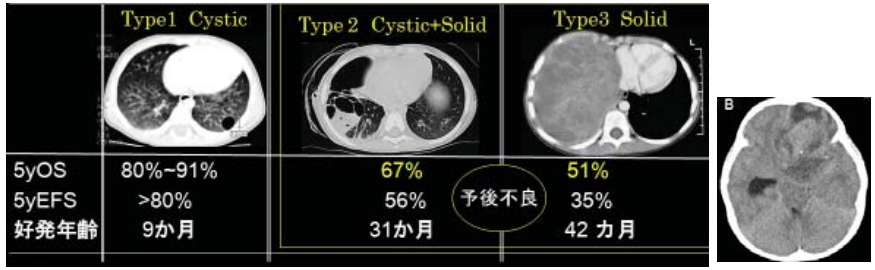
Science. 2009 ; 21(325):965

DICER1 Mutations in Familial Pleuropulmonary Blastoma

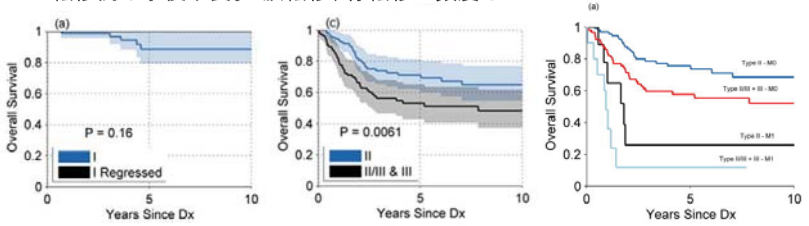
D. Ashley Hill, Jennifer Ivanovich, John R. Priest, Christina A. Gurnett, Louis P. Dehner, David Desruisseau, Jason A. Jarzembowski, Kathryn A. Wikenheiser-Brokamp, Brian K. Suarez, Alison J. Whelan, Gretchen Williams, Dawn Bracamontes, Yoav Messinger and Paul J. Goodfellow



Pleuropulmonary blastoma (PPB) 胸膜肺芽腫について



- ✓ 胸膜原発の稀な小児悪性腫瘍。Type1,2,3に分類される。
- ✓ 治療はGTR, type2,3については化学療法(VCR, DOX,CYA,IFO,ETP,ActD etc)
- ✓ 転移例は予後不良。 脳転移、骨転移の頻度は25%、10%

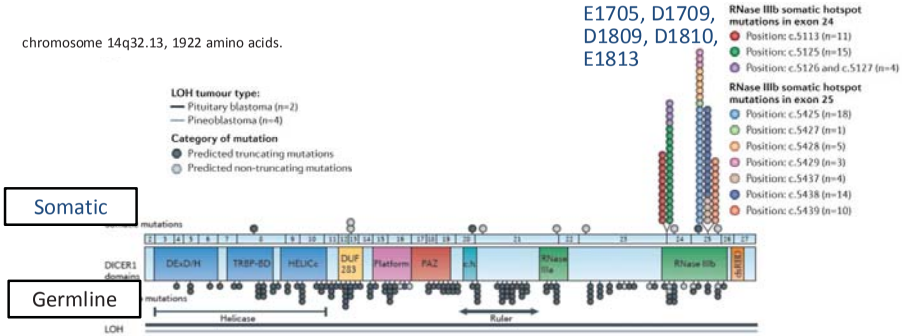


PPB registry http://www.ppbregistry.org/
Messinger YH, et al. Cancer. 2015;15;121:276-85.

DICER1 syndromeにおける*DICER1* mutationの特徴

chromosome 14q32.13, 1922 amino acids.

E1705, D1709, D1809, D1810, E1813



- ✓ Tumor specific missense mutation at one of five "hotspot" codons within the RNase Ⅲb domain of DICER1, combined with germline loss of function (LOF) in the other allele.
- ✓ Over 70% of Pts with PPB have these mutations.
- ✓ 60 % of Pts with Sertoli-Leydig cell tumors and 29% of nonepithelial ovarina tumors have DICER1 mutations in the RNaseⅢb domain.
- ✓ Approximately 10% of predisposing DICER1 mutations are mosaicism for either LOF or RnaseⅢb hotspot mutations.

Foulkes WD, et al. Nat Rev Cancer. 2014 ;14:662-72.
Brenneman M, et al. F1000Research. 2015;4:214
Schultz KAP, et al.Clin Cancer Res. 2018
Hervai0Moussavi A, et al. NEJM. 2012;366:234-42.

Phenotype and relative frequency*	Is *DICER1* mutation testing indicated following a diagnosis?[2]	Approximate range for age of susceptibility (peak)	Malignant (M) or benign (B)	Deaths associated?
Most frequent phenotypes[3]				
Type I (cystic) PPB	Yes	0–24 months (8 months)	M	Yes, if it progresses to type II or III
Type II (cystic/solid) PPB	Yes	12–60 months (31 months)	M	Yes, ~40%
Type III (solid) PPB	Yes	18–72 months (44 months)	M	Yes, ~60%
Type Ir (cystic) PPB	Yes	Any age	B or M**	None observed**
MNG	No	5–40 years (10–20 years)	B	No
Cystic nephroma	Yes	0–48 months (undetermined)	B	No (see ASK, below)
SLCT of ovary	Yes	2–45 years (10–25 years)	M	Yes, <5% of cases
Moderate frequency phenotypes[3]				
cERMS	Yes	4–45 years (10–20 years)	M	None observed
Rare frequency phenotypes[3]				
DTC	No	5–40 years (10–20 years)	M	None observed
Wilms' tumour	No	3–8 years (undetermined)	M	None observed
Juvenile hamartomatous intestinal polyps	No	0–4 years (undetermined)	B	No
CBME	Yes	3–10 years (undetermined)	B or M[33]	None observed
NCMH	Yes	6–18 years (undetermined)	B	No
Pituitary blastoma (PitB)	Yes	0–24 months (undetermined)	Undetermined[28]	Yes, ~50%[28]
Pineoblastoma (PinB)	Yes	2–25 years (undetermined)	M	Yes
Very rare phenotypes[4]				
ASK	Yes	Estimated 2–20 years	M	Yes
Medulloblastoma	No	Undetermined	M	Unknown
ERMS of the bladder	No	Estimated <5 years	M	None observed
oERMS	Yes	Undetermined	M	None observed
Neuroblastoma	No	Estimated <5 years	M	Yes
Congenital phthisis bulbi	No	Birth	B	No
OSCST juvenile granulosa cell tumour	Undetermined	Undetermined	M	None observed
OSCST gynandroblastoma	Undetermined	Undetermined	M	None observed
Cervix primitive neuroectodermal tumour	Undetermined	Undetermined	M	None observed

Foulkes WD, et al. Nat Rev Cancer. 2014 ;14:662-72.

頻度の高い悪性腫瘍はPPB, Cystic nephroma, SLCT of ovary等
好発時期はearly childhoodのものが多いが40代に発症するものもある。

目次

I. DICER1 syndrome の概要

II. Recommendations for testing and surveillance DICER1 AACR review

III. PPB registry の紹介 と DICER1 summit,2017 の報告

IV. 日本のPPB, DICER1 syndrome について + 今後？

- Prevalence やpenetrance はunknownなところが多い…

✓ Inherited as autosomal dominant condition with decreased penetrance.
✓ Penetrance of phenotypes is not known (15% or less?)
✓ At least 50% of female carries and perhaps 80% of male carriers seem to be clinically unaffected.

Foulkes WD, et al. Nat Rev Cancer. 2014 ;14:662-72.

The prevalence of *DICER1* pathogenic variation in population databases

Jung Kim[1], Amanda Field[2], Kris Ann P. Schultz[3,4,5], D. Ashley Hill[2,6] and Douglas R. Stewart[1]

[1] Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD
[2] Division of Pathology and Center for Genetic Medicine Research, Children's National Health System, Washington, DC
[3] Cancer and Blood Disorders, Children's Hospitals and Clinics of Minnesota, Minneapolis, MN
[4] International Pleuropulmonary Blastoma Registry, Minneapolis, MN
[5] International Ovarian and Testicular Stromal Tumor Registry, Minneapolis, MN
[6] Department of Integrative Systems Biology, George Washington University School of Medicine and Health Sciences, Washington, DC

The *DICER1* syndrome is associated with a variety of rare benign and malignant tumors, including pleuropulmonary blastoma (PPB), cystic nephroma (CN) and Sertoli-Leydig cell tumor (SLCT). The prevalence and penetrance of pathogenic *DICER1* variation in the general population is unknown. We examined three publicly-available germline whole exome sequence datasets: Exome Aggregation Consortium (ExAC), 1,000 Genomes (1,000 G) and the Exome Sequencing Project (ESP). To avoid overestimation of pathogenic *DICER1* variation from cancer-associated exomes, we excluded The Cancer Genome Atlas (TCGA) variants from ExAC. All datasets were annotated with snpEff and ANNOVAR and variants were classified into four categories: likely benign (LB), unknown significance (VUS), likely pathogenic (LP), or pathogenic (P). The prevalence of *DICER1* P/LP variants was 1:870 to 1:2,529 in ExAC-nonTCGA (53,105 exomes) estimated by metaSVM and REVEL/CADD, respectively. A more stringent prevalence calculation considering only loss-of-function and previously-published pathogenic variants detected in ExAC-nonTCGA, yielded a prevalence of 1:10,600. Despite the rarity of most *DICER1* syndrome tumors, pathogenic *DICER1* variation is more common than expected. If confirmed, these findings may inform future sequencing-based newborn screening programs for PPB, CN and SLCT, in which early detection improves prognosis.

Int. J. Cancer: 141, 2030–2036 (2017) 2017 UICC

CCR PEDIATRIC ONCOLOGY SERIES

PTEN, DICER1, FH, and Their Associated Tumor Susceptibility Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood

Kris Ann P. Schultz[1], Surya P. Rednam[2], Junne Kamihara[3], Leslie Doros[4], Maria Isabel Achatz[5], Jonathan D. Wasserman[6], Lisa R. Diller[7], Laurence Brugières[8], Harriet Druker[9,10], Katherine A. Schneider[11], Rose B. McGee[12], and William D. Foulkes[13]

June-2017

Table 1. Key clinical phenotypes associated with germline *DICER1* pathogenic variants

Phenotype and relative frequency	Approximate ages of susceptibility range (peak)	Malignant (M) or benign (B)	
Most frequent phenotypes			
PPB			
Type I (cystic) PPB	0–24 m (8 m)	M	
Type II (cystic/solid) PPB	12–60 m (31 m)	M	
Type III (solid) PPB	18–72 m (44 m)	M	
Type Ir (cystic) PPB	Any age	B or M	
Multinodular goiter[4]	5–40 y (10–20 y)	B	
Cystic nephroma	0–48 m (undetermined)	B	n (see anaplastic sarcoma of kidney below)
Sertoli-Leydig cell tumor of ovary	2–45 y (10–25 y)	M	y, <5% of cases
Moderate frequency phenotypes			
Cervix embryonal rhabdomyosarcoma	4–45 y (10–20 y)	M	None observed
Rare frequency phenotypes			
DTC	5–40 y (10–20 y)	M	None observed
Wilms tumor	3–13 y (undetermined)	M	None observed
Juvenile hamartomatous intestinal polyps	0–4 y (undetermined)	B	n
Ciliary body medulloepithelioma	3–10 y (undetermined)	B or M	None observed
Nasal chondromesenchymal hamartoma	6–18 y (undetermined)	B	n
Pituitary blastoma	0–24 m (undetermined)	Undetermined	y, ~50%
Pineoblastoma	2–25 y (undetermined)	M	y
Very rare phenotypes			
Anaplastic sarcoma of kidney	Estimated 2–20 y	M	y
Medulloblastoma	Undetermined	M	Unknown
ERMS bladder	Estimated <5 y	M	None observed
ERMS ovary	Undetermined	M	None observed
Neuroblastoma	Estimated <5 y	M	y
Congenital phthisis bulbi	Birth	B	n
Juvenile granulosa cell tumor	Undetermined	M	None observed
Gynandroblastoma	Undetermined	M	None observed
Cervix primitive neuroectodermal tumor	Undetermined	M	None observed

***DICER1* syndrome cancer screening/surveillance protocols and recommendations**

Indications for consideration of *DICER1* gene testing include a new diagnosis of most, if not all, the conditions in Table 1, or any childhood tumor in association with a personal or family history of *DICER1*-related conditions. In 2016, the International *DICER1* Symposium convened to establish recommendations for testing and surveillance guidelines for individuals with *DICER1* pathogenic variants (K.A.P. Schultz; article in preparation). Consensus recommendations from the 2016 AACR Childhood Cancer Predisposition Workshop are summarized here.

June-2017のreviewでは、
・ Genetic testing はTable1に挙げられた疾患の most if not at all で検討すべしと記載されている。
（Table1は2014年のNature review）
・ 今後、International DICER1 symposiumからrecommendationが出されると書いていた。

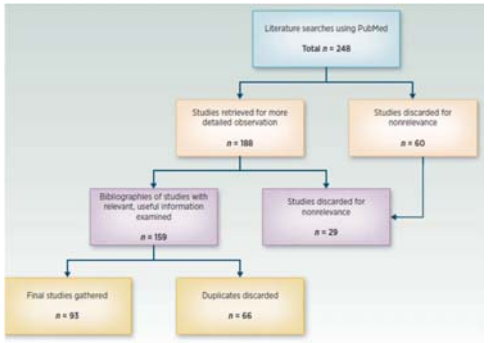
***DICER1* and associated conditions: Identification of at-risk individuals and recommended surveillance strategies**

Kris Ann P. Schultz[1,2,3], Gretchen M. Williams[1,2,3], Junne Kamihara[4], Douglas R. Stewart[5], Anne K. Harris[1,2,3], Andrew J. Bauer[6], Joyce Turner[7], Rachana Shah[8], Katherine Schneider[9], Kami Wolfe Schneider[10], Ann Garrity Carr[11], Laura A. Harney[11], Shari Baldinger[12], A. Lindsay Frazier[4], Daniel Orbach[13], Dominik T. Schneider[14], David Malkin[15], Louis P. Dehner[16], Yoav H. Messinger[1,2,3], D. Ashley Hill[17]

Jan-2018, AACR online

Methodology:

- Data from the international PPB and OTST registers ⇒ 682 individuals from 652 families.
- Pub med literature search



Searches on PubMed using keyword(s) and *DICER1*

Search keywords	Returns
pleuropulmonary blastoma	68
Sertoli-Leydig cell tumor	50
gynandroblastoma	23
juvenile hamartomatous polyp	1
cystic nephroma	30
multinodular goiter	18
thyroid adenoma	13
thyroid carcinoma	16
ciliary body medulloepithelioma	8
botryoid embryonal rhabdomyosarcoma (ERMS) of the cervix or other sites	1
nasal chondromesenchymal hamartoma	6
renal sarcoma	7
pituitary blastoma	2
pineoblastoma	5

Indications for DICER1 genetic counseling and testing

- Recommend genetic counseling and testing for individuals with a personal history of at least one major or two minor indications for testing.

Major:	Minor:
-Individuals with PPB (all types) -Lung cyst(s) in childhood, especially if multi-septated, multiple or bilateral -Thoracic embryonal rhabdomyosarcoma*	-Lung cyst(s) in adults -Renal cyst(s)* -Wilms tumor
-Cystic nephroma -Genitourinary sarcomas including undifferentiated sarcoma*	-Multinodular goiter or differentiated thyroid cancer -Embryonal rhabdomyosarcoma other than thoracic or gynecologic*
-Ovarian Sertoli-Leydig cell tumor -Gynandroblastoma -Uterine cervical or ovarian embryonal rhabdomyosarcoma* -Genitourinary/gynecologic neuroendocrine tumors	-Poorly differentiated neuroendocrine tumor -Undifferentiated sarcoma*
- Multinodular goiter or thyroid cancer in 2 or more 1st degree relatives or in an index patient with a family history consistent with *DICER1* syndrome*	-Macrocephaly* -Consider testing for any childhood cancer in constellation with any other minor criteria
-Childhood onset multinodular goiter* or differentiated thyroid cancer*	
-Ciliary body medulloepithelioma	
-Nasal chondromesenchymal hamartoma	
-Pineoblastoma -Pituitary blastoma	

* Multinodular goiter, differentiated thyroid cancer (papillary or follicular carcinomas), sarcomas, Wilms tumor, neuroendocrine tumors, renal cysts and macrocephaly may also be associated with other genetic predisposition syndromes. Consider testing for additional hereditary cancer predispositions and/or next generation sequencing panel that includes deletion/duplication of *DICER1* and/or other genes indicated by clinical and family history

- In cases where proband testing is not feasible, testing should be considered for those with family history of DICER1-associated conditions so that appropriate surveillance can be undertaken.
- Individuals at 50% risk of germline pathogenic variant based on family history who do not pursue genetic testing should follow surveillance guidelines unless/until genetic testing confirms that they did not inherit the familial mutation.
- For individuals with pathogenic germline DICER1 variants, additional site-specific genetic testing of that variant for all first-dgree relatives is recommended. Testing should be prioritized in children less than 7 years of age, who are at greatest risk for any one of the pathogenic type of PPB.
- Recommendations for testing must also consider the role of DICER1 in individual tumor types. However, since genetic testing is shifting from single gene to panel testing, it may be appropriate to add DICER1 gene testing if a child with Wilms tumor or another DICER1-related tumor is being tested for genes.

Testing algorithm

- If no mutation is detected via DICER1 sequencing in a germline specimen, germline DICER1 deletion/duplication analyses should be performed.
- The possibility of mosaichism may be considered with testing of other normal tissue, tumor tissue, or future children.

Timing of testing

- For newborns, testing is recommended before 4 months of age so that pulmonary screening can be initiated only in at risk infants.

Prenatal management

- Third trimester US for women whose fetuses are at risk for pathogenic DICER1 variant to detect large lung cysts which might require early intervention after delivery.
- Prenatal US has a higher sensitivity for cystic lung disease than neonatal chest x-ray.

Screening recommendations for Dicer1-associated conditions by system

System	Signs/Symptoms to consider	Condition of interest	Screening, Clinical and Radiographic
Lung	Tachypnea, cough, fever, and pain; pneumothorax	- PPB - Lung cysts -Pulmonary blastoma	CXR at birth and every 4- 6 months until 8 years of age, every 12 months 8 -12 years of age; consider a CT of chest at 3 - 6 months of age.* Toddlers: if initial CT normal: repeat between 2-1/2 and 3 years of age.* If mutation detected at > 12 years of age, consider baseline CXR or chest CT.
Thyroid	Visible or palpable thyroid nodule(s) Persistent cervical lymphadenopathy Hoarseness Dysphagia Neck pain Cough	- Multinodular goiter; - Differentiated thyroid cancer	Baseline thyroid US by 8 years of age then every 3 years or with symptoms/findings on physical exam. *With anticipated chemotherapy or radiation therapy: baseline US and the annually for 5 years, decreasing to every 2 to 3 years if no nodules are detected*

- At Birthのcyst　PPB type2,3の好発時期を逃さないよう。
- 所見のない児のCTは2回。

- Individuals with one or more DICER1-associated condition show that by 20 years of age, the cumulative incidence of multinodular goitor or history of thyroidectomy is 32% in women and 13% in men.
- 16- to 24- fold increased risk of thyroid cancer.

Female reproductive tract	Hirsutism Virilization Abdominal distension, pain or mass	- SLCT - Gynandroblastoma - Cervical embryonal rhabdomyosarcoma	For females beginning at 8 – 10 years of age: pelvic and abdominal US every 6-12 months at least until age 40. *End of interval is undetermined but current oldest patient with DICER1-associated SLCT was 61 years of age. Education regarding symptoms strongly recommended.*
Renal	Abdominal or flank mass and/or pain, hematuria	- Wilms tumor - Renal sarcoma - Cystic nephroma	Abdominal US every 6 months until 8 years of age then every 12 months until 12 years of age. If mutation detected at > 12 years of age, consider baseline abdominal US
Gastrointestinal	Signs of intestinal obstruction	- Small intestine polyps	Education regarding symptoms recommended.
Central nervous system And head and neck (excluding thyroid)	Headache, emesis, diplopia, decreased ability for upward gaze, altered gait (pineoblastoma); Precocious puberty; Cushing's syndrome (pituitary blastoma); Decreased visual acuity and leukocoria (CBME); Nasal obstruction (NCMH)	- Macrocephaly - Pineoblastoma - Pituitary blastoma - CBME - NCMH	Physical exam. Annual routine dilated ophthalmologic exam (generally unsedated) with visual acuity screening from 3 years of age through at least 10 years of age. Further testing if clinically indicated. Recommend urgent MRI for any symptoms of intracranial pathology.

- Age distribution of risk for SLCT is wide from 4 to 61 years of age (median 16.9 years) in OTST registry. Education !

The role of surveillance imaging by MRI remains controversial.

- The most severe manifestations of pathogenic germline DICER1 variants tend to present in early childhood and with adulthood characterized by good health.
- Some tumors are curable with surgery alone when found in their earliest stage.
- Risks and potential benefits of lifelong screening must be carefully balanced.
- Family and health care provider education!

DICER1 syndrome: Approach to testing and management at a large pediatric tertiary care center

SickKidsからの報告

Kalene van Engelen[1] | Anita Villani[2,3] | Jonathan D. Wasserman[3,4] | Laura Aronoff[2,5] | Mary-Louise C. Greer[6] | Marta Tijerin Bueno[6] | Bailey Gallinger[1,7,8,9] | Raymond H. Kim[7,10] | Ronald Grant[2,3] | M. Stephen Meyn[1,3,7,9] | David Malkin[1,2,3] | Harriet Druker[2,8,9]

Pediatr Blood Cancer. 2018;65(1).

- Clinical surveillance, follow-up duration is 23 mo.
⇒ 8 asymptomatic lesions were detected in seven of 14 Pts undergoing surveillance protocol at SickKids. Identified PPB in tow asymptomatic individuals were resected and the patients remained disease free.

TABLE 5 Institutional surveillance guidelines for *DICER1* pathogenic variant carriers

Baseline CT Chest at birth/diagnosis Chest X-ray q6m to age 8, annually to age 18	Pleuropulmonary blastoma
Abdominal/pelvic ultrasound from birth/diagnosis q6m until age 40	Cystic nephroma/Wilms tumor, gynecologic tumors
Thyroid palpation annually from age 10[a]. If concerning features (see text) are noted, obtain neck/thyroid ultrasound and consider pediatric endocrine referral if radiographic concerns	Nodular thyroid hyperplasia and carcinoma
MRI brain annually from diagnosis/birth to age 25	Pineoblastoma/pituitary blastoma
Annual physical exam with specific inquiry and assessment for visual changes, leukocoria, lens changes, and persistent nasal obstruction/hyposmia/rhinorrhea. Consider specialist referral (ophthalmology/otorhinolaryngology) for any identified concerns.	

[a]Individuals previously exposed to alkylating chemotherapy should commence thyroid ultrasound surveillance 5 years post completion of chemotherapy, or at age 10, whichever comes first, with ongoing imaging every 2–3 years.

TABLE 4 Criteria for *DICER1* genetic testing

DICER1 genetic testing should be pursued in any of the following scenarios:

- The individual presents with any of the following:
  - Pleuropulmonary blastoma
  - Familial multinodular goiter[a]
  - Cystic nephroma
  - Sertoli–Leydig cell tumor
  - Pineoblastoma
  - Gynecological and bladder embryonal rhabdomyosarcoma
  - Ciliary body medulloepithelioma
  - Nasal chondromesenchymal hamartoma
  - Pituitary blastoma
  - Anaplastic sarcoma of the kidney
  - Congenital pulmonary airway malformation
  - Juvenile granulosa cell tumor
  - Gynandroblastoma
- A first-degree relative is affected by one of the above and is unavailable for testing
  - The individual presents with any tumor in childhood and a family history of DICER1 features
- There is a confirmed *DICER1* variant in the family

[a]Consider genetic testing for an isolated case of pediatric multinodular goiter.
Although the prevalence of germline *DICER1* pathogenic variants among children with multinodular goiter is unknown, genetic testing in these cases may be considered.

目次

I. DICER1 syndrome の概要

II. Recommendations for testing and surveillance DICER1 AACR review

III. PPB registry の紹介 と DICER1 summit,2017 の報告

IV. 日本のPPB, DICER1 syndrome について + 今後？

International Meeting のinvitationが来たので
行ってみました。

International Pleuropulmonary Blastoma (PPB) Collaborative Discussion

Friday, October 9, 2015

SIOP – Cape Town 2015 Meeting

Location: Room 1.62 ITCC 2:00 – 6:00 pm

AGENDA

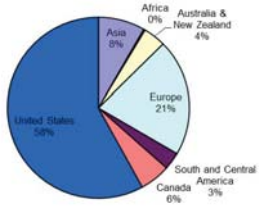
Presentations:

1. Ashley Hill – DICER1 and PPB. New up to date data, including PPB cell-line data. Web based presentation
2. Yoav Messinger – Clinical data from the IPPBR, including updated IVADo results to date
3. Gianni Bisogno – The EXPORNET project
4. Daniel Orbach – The EXPeRT/EXporNET PPB guidelines
5. Kris Ann Schultz – Clinical and Genetic Aspects of Ovarian Sex Cord-Stromal Tumors: A Report from the International OTST Registry

2015年:
First PPB international meeting

2016年:
Consensus guidelineの作成

2017年: Clinical and collaborationと
researchの成果



Argentina	China	Germany
Australia	Columbia	Hong Kong
Austria	Czech Republic	India
Bahrain	Egypt	Ireland
Belgium	England	Israel
Brazil	Finland	Italy
Canada	France	Japan
Kuwait	Puerto Rico	Sweden
Mexico	Russia	Switzerland
Morocco	Saudi Arabia	Taiwan
Netherlands	Scotland	Tunisia
New Zealand	Singapore	Ukraine
Philippines	South Korea	United States
Portugal	Spain	Viet Nam

PPB registryは症例の中央病理診断、遺伝子診断などを担う。
症例のコンサルトにも応じる。

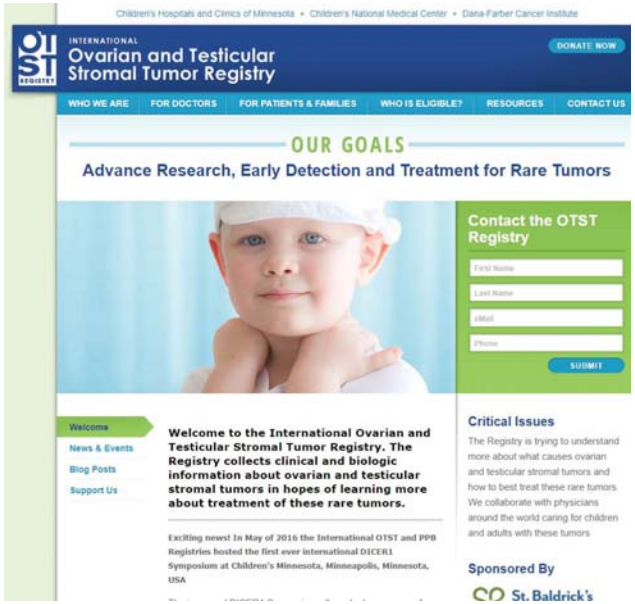
PPB registry http://www.ppbregistry.org/
Messinger YH, et al. Cancer. 2015;15;121:276-85.

Results of IPPBR Central Pathology Review

Year of diagnosis	PPB Confirmed	PPB Ruled-out	Total IPPBR Reviewed
≤ 1979	13	Not tracked	13
1980 - 1989	18	Not tracked	18
1990 - 1999	73	8 (10%)	81
2000 - 2009	196	50 (20%)	246
2010 - May 2012	50	27 (35%)	77
Total	350	85 (20%)	435

PPBの病理診断の正診率は80%

Ruled Out Diagnosis	n
Benign Cystic Lesions	
Fetal Lung Interstitial Tumor (FLIT)	11
Congenital Pulmonary Adenomatoid Airway Malformation (CPAM)	7
Lung Cysts	3
Malignancy	
Rhabdomyosarcoma	11
Pulmonary Blastoma	6
Spindle cell Sarcoma	5
Synovial Sarcoma	3
Undifferentiated sarcoma or small round cell tumor	11
Ewing's, PNET*, Askin's tumor	3
Teratoma, Yolk-sac tumor	5
Fibrosarcoma, Fibromyxoid sarcoma	4
Malignant - Others	10
Other Lesions	
Hemangiopericytoma & Mesenchymal Hamartoma	2
Carcinoma or epithelial neoplasm	2
Histiocystic infiltrate	1
Bronchiectasis	1
Total	85



DICER1: From the pathology trenches	Sara O. Varges, MD Staff Pathologist, Boston Children's Hospital Associate Professor, Harvard Medical School
New approaches to modeling DICDER1 missense mutations	James Amatruda, MD, PhD Hematology/Oncology University of Texas Southwestern
Molecular effects of DICER1 mutations	Kenneth Chen, MD Hematology/Oncology, University of Texas Southwestern
Biomarkers for disease emergence and treatment response	Ashley Hill, MD Department of Pathology Children's National International PPB Registry Mark Brenneman, PhD Department of Pathology, Center for Cancer and Immunology Research Children's National
Establishment of PPB PDX mouse models and cell lines for preclinical studies of targeted therapies	Weiying Yu, MD, Chenyu Xu, PhD Center for Cancer and Immunology Research Children's National

- PDX の作成に成功
- まだtarget therapyは難しそう
- Liquid biopsyの試み

Group discussion
-Improving outcomes in Type2 and 3 PPB
-Ideas for reducing radiation in surveillance
-Early findings form surveillance strategies
-Management of small lung cysts in young children

DICER1 SUMMIT 14-Oct-2017. AGENDA

2017 SIOPと併せて開催された4時間のmeeting. PPB, OTST registryのコアメンバー, Ashley 's labの学生。Europeのrare tumor group, ロシアと日本から一人ずつ. Total 25人くらい

TOPIC	PRESENTOR
Welcome and introductions	Kris Ann P Schlutz, MD International PPB and OTST registers Children's Minnesota
The challenging of very rare tumors in Europe	Prof. Gianni Bisogno Dept. of Women's and Child's Health Universita of Padova, Padova Italy
Genetics of DICER1 syndrome: a French retrospective study of 204 analysis	Daniel Orbach, MD Oncology Center SIREDO, Institute Curie Medical Center, Paris, France
More common than you thought: The prevalence of DICER1 pathogenic variation in general population and cancer databases	Jung Kim, PhD Clinical Genetics Branch Div. of Cancer Epidemiology and Genetics National Cancer Institute, Rockville, MD
Genotype first, phenotype second: Novel phenotype discovery in the Dicer1 syndrome in the era of large-scale exome sequencing	Douglas R. Stewart, MD Clinical Genetics Branch Division of Cancer Epidemiology and Genetics National Cancer Institute, Rockville, MD
An update from the international PPB/DICER1 and OTST registries	Kris Ann P Schlutz, MD International PPB Minnesota

- Europeのrare tumorの取組み
- SLCT, DICER1 mt(+)の母から生まれた新生児にDICER1 testingをすることによりのPPBを早期発見、治療ができたという報告

The challenge of very rare tumors in Europe

Prof. Gianni Bisogno
Department of Women's and Child's Health
Università of Padova, Padova Italy

ExPO-r-Net is a 3-year project that will build a European Reference Network (ERN) for Paediatric Oncology. ExPO-r-NeT aims to reduce the current inequalities in childhood cancer survival and healthcare capabilities in different EU Member States.

The European Cooperative Study Group for Pediatric Rare Tumors

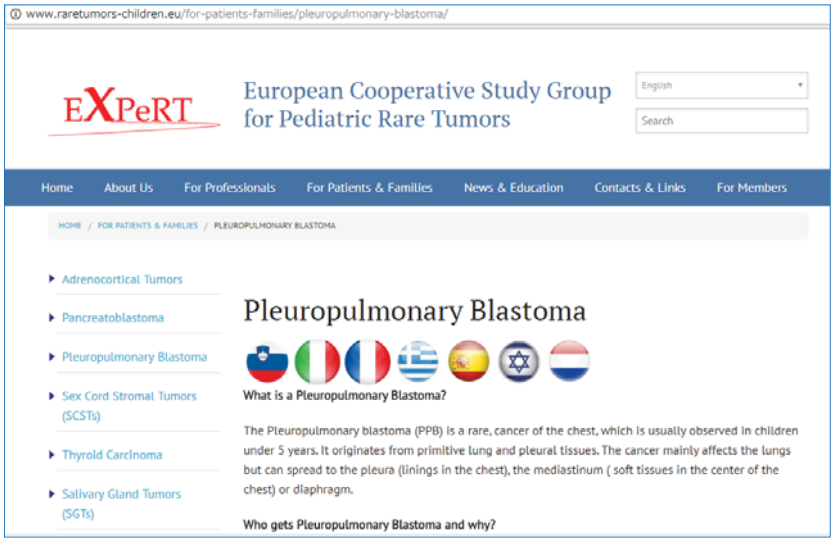
http://www.raretumors-children.eu/

Since 2015.
Guideline for Rare tumor作成。
医療者への情報提供、internet-consultation受付。
-The VRT-VTB project
患者への情報提供。

-rare tumorは恐らく医者をしていて1-2例くらいしかみる機会はない。

Adrenocortical tumors
Carcinoid of the appendix
Gonadal, non germ cell, tumors
Nasopharyngeal carcinoma
Pancreatic tumors
Pheochromocytoma and paraganglioma
Pleuropulmonary blastoma
Renal carcinoma
Skin tumors like melanoma
Salivary gland tumors
Thymic tumors
Thyroid carcinoma

*This list is not exhaustive and need to be continuously updated because newly discovered entities need to be added.



- ✓ 8言語での説明　about PPB for Pts and families がavailable
- ✓ 設立前にこのようなシステムをもっていた国はEuropeanの30%
- ✓ これまでのPPB症例(diagnosed or expected)は0-5 cases/country （数年間）
- ✓ EU groupになれば120例くらいはいる。(48例がIPPR registry)

日本からの報告

表1　本邦の報告例

発表年	報告者	年　齢	肺嚢胞性疾患	手　術	化学療法	放射線療　法	転　帰
1976	小平[11]	10 歳	無	右上葉切除	−	−	生(7年)
1981	秋山[12]	1 歳7ヶ月	有	副葉切除	VAC	○	死(1年10ヶ月)
1983	大友[13]	3 歳	有	右下葉摘出	VAC+Adr	○	死(6ヶ月)
1983	大友	3 歳	無	左下葉摘出	VAC+Adr	−	生(16年)
1984	中野[14]	2 歳	有	腫瘤核手術	VCR+Cy+MTX	−	生(1年4ヶ月)
1986	矢野[15]	2 歳4ヶ月	有	右中葉切除	VAC	○	生(1年)
1987	貝志堅[16]	3 歳	無	右中下葉切除	VAC+Adr	−	生
1989	金子[17]	3 歳	無	腫瘤摘出術	VAC	○	生(1年4ヶ月)
1995	雨海	2 歳6ヶ月	無	腫瘤摘出術	NWTS	−	生(3年1ヶ月)
1995	古野[18]	1 歳6ヶ月	無	右中下葉切除	NWTS	○	死(1年)
1996	山下[19]	40 日	無	左下葉切除	NWTS	−	生(1年)
1997	井上[20]	2 歳7ヶ月	無	左下葉切除	Double PBSCT	−	生(1年7ヶ月)
1998	草深[21]	1 歳10ヶ月	有	右中葉部分切除		−	死(7ヶ月)
1999	黒田[22]	2 歳	無	腫瘤摘出術			死(11ヶ月)
1999	黒田[23]	2 歳7ヶ月	無	左肺全摘	PBSCT	−	死(1年3ヶ月)
1999	岡崎[24]	3 歳3ヶ月	無	右中葉切除	VCR,ACD,CPM,Adr	−	生(2ヶ月)
1999	竹谷[25]	2 歳7ヶ月	有	腫瘤摘出術	PBSCT	○	死(3年7ヶ月)
1999	竹谷	2 歳7ヶ月	無	腫瘤摘出術	VAC+Adr	○	死(1年5ヶ月)
2001	石川[26]	2 歳	無	左肺全摘	VCR,CDDP,VP-16,Adr	−	生(5ヶ月)
2001	加藤[27]	1 歳6ヶ月	有	腫瘤摘出術	Double PBSCT	−	生(2ヶ月)
2001	飯塚[28]	2 歳1ヶ月	無	右中葉切除	横紋筋肉腫（大平組）	−	生(1年)
2001	近藤[29]	2 歳	無	腫瘤摘出術	PBSCT	−	生(2年)
2002	高橋[30]	2 歳4ヶ月	無	腫瘤摘出術	VAC	−	生(10ヶ月)
2002	岩井[31]	11 歳	無	手術なし	PBSCT	−	死(5ヶ月)
2002	岩井	1 歳	無	手術なし	VCR,ACD,Adr	−	死(2ヶ月)
2002	黒田[32]	3 歳6ヶ月	有	腫瘤摘出術	Double PBSCT	−	生(8ヶ月)
2003	林[33]	3 歳	無	中下葉切除	PBSCT 研究会プロトコール	−	死
2003	本症例	2 歳8ヶ月	有	腫瘤摘出術	PBSCT	○	生(7ヶ月)
		平均 34.5ヶ月	9例 (32%)			8例	

小児がん　41巻 124-129. 2004

- ✓ 本邦では約60例のPPBの報告がある(2015年,小児がん学会抄録)。
- ✓ 医中誌で“胸膜肺芽腫”で検索すると107例（重複例あり、多くが会議録/症例報告）
- ✓ 診断時年齢が10歳以上の症例も含まれている。
- ✓ 治療方法も様々。

目次

- ✓ 本邦の症例報告から抜粋

DICER1 syndromeが疑われる経過や　f/uの重要性を示唆するPPB症例

	Title	Year	Journal/ meeting	Clinical course
1	胸膜肺芽腫術後に発症した甲状腺癌女児例	2005	小児腫瘍分類委員会症例検討会	3歳時にPPBを発症。6歳時に頸部腫瘤から甲状腺濾胞がんと診断。母に甲状腺腫。
2	末梢血幹細胞移植を併用した大量化学療法を含む集学的治療施行後、腺腫様甲状腺腫を発症した胸膜肺芽腫の1例	2015	日本小児外科学会雑誌	2歳時にPPBを発症。6歳時に頸部腫瘤⇒甲状腺亜全摘、腺腫甲状腺腫。母に甲状腺腫。
3	胸膜肺芽腫の5例	2015	日本小児血液・がん学会	5例中1例に嚢胞性腎腫、2例に甲状腺腫。
4	小児固形腫瘍治療後に発生した二次性甲状腺癌の4例	2017	日本小児血液・がん学会雑誌	1歳時にPPBを発症。10歳時に前頸部腫脹を契機に甲状腺濾胞がん(T2NXM0,stage1)⇒甲状腺右葉切除、頸部リンパ節郭清
5	同胞発症した胸膜肺芽腫Typeiiの2例	2017	日本臨床細胞学会雑誌	N/A
6	Pneumatoceleの経過観察中に発見された胸膜肺芽腫の一例	2009	小児がん学会雑誌	0歳2か月時に左肺上下葉に肺嚢胞性病変が認められフォローされていた。3歳時に腫瘤性病変が出現。PPBと診断、化学療法、大量化学療法を施行(TEPA/L-PAM)。
7	20年を経て子宮頸部に転移再発した小児胸膜肺芽腫の1例	2006	日本産婦人科学会	2歳時にPPBを発症。20歳時に子宮頸部にポリープ様の病変が多発しmetastatic pleuropulmonary blastomaの診断。円錐切除術⇒病理標本で断端陽性のために子宮全摘、VAC療法を施行。

Biallelic *DICER1* Mutations in Sporadic Pleuropulmonary Blastoma

Masafumi Seki[1], Kenichi Yoshida[2,6], Yuichi Shiraishi[3], Teppei Shimamura[3], Yusuke Sato[2,6], Riki Nishimura[1], Yusuke Okuno[2], Kenichi Chiba[3], Hiroko Tanaka[4], Keisuke Kato[7], Motohiro Kato[1,5,8], Ryoji Hanada[5], Yuko Nomura[9], Myoung-Ja Park[10], Toshiaki Ishida[11], Akira Oka[1], Takashi Igarashi[1,12], Satoru Miyano[3,4], Yasuhide Hayashi[9], Seishi Ogawa[2,6], and Junko Takita[1]

Abstract

Pleuropulmonary blastoma (PPB) is a rare pediatric malignancy whose pathogens are poorly understood. Recent reports suggest that germline mutations in the microRNA-processing enzyme DICER1 may contribute to PPB development. To investigate the genetic basis of this cancer, we performed whole-exome sequencing or targeted deep sequencing of multiple cases of PPB. We found biallelic *DICER1* mutations to be very common, more common than *TP53* mutations also found in many tumors. Somatic ribonuclease III (RNase IIIb) domain mutations were identified in all evaluable cases, either in the presence or absence of nonsense/frameshift mutations. Most cases had mutated *DICER1* alleles in the germline with or without an additional somatic mutation in the remaining allele, whereas other cases displayed somatic mutations exclusively where the RNase IIIb domain was invariably affected. Our results highlight the role of RNase IIIb domain mutations in *DICER1* along with TP53 inactivation in PPB pathogenesis. *Cancer Res; 74(10); 2742–9. ©2014 AACR.*

Table 1. Mutations in *DICER1* and *TP53* in sporadic PPB cases

	DICER1				*TP53*				
Case	Exon	Mutation	AA change	Origin	Exon	Mutation	AA change	17p	Sample
01	25	5428G>T	D1810Y	Somatic		Native		Loss	Pr/Re
02		Native				Native			Pr/Re
03	23	4910C>A	S1637X	ND	4	c.332_333delTG	p.L111fs	Loss	Pr
	24	5114A>T	E1705V	ND					
04	21	3482delC	P1161fs	Germline	5	c.527G>T[a]	p.C176F	Loss	Pr/Re
	24	5125G>A	D1709N	Somatic	4	c.313G>A[b]	p.G105S		
05	9	1383delAAAG	H461fs	Germline		Native			Pr
06	19	3007C>T	R1003X	ND		Native			Pr
	25	5428G>T	D1810Y	Probably somatic					
07	18	2863insA	T955fs	Germline	8	c.891_903	p.H297fs	Loss	Pr
	25	5425G>A	G1809R	Somatic		delCGAGCTGCCCCCA			
08	21	3748delC	S1250fs	Germline	7	c.762_764delACAT	p.I254fs	Loss	Pr
	25	5425G>A	G1809R	Somatic					
09	25	5425G>A (Homozygous)	G1809R	Somatic		Native		Loss	Pr
10	25	5425G>A (Homozygous)	G1809R	Somatic	8	c.817C>T	p.R273C	Loss	Pr/Re
11	8	1148dupAGGGT	I383fs	ND		Native		ND	Pr
12	25	5460C>G	Y1820X	Germline		Native		Loss	Pr
	25	5438A>G	E1813G	Somatic					

PPB educational information

Nov-2017 ,
Kris Ann Schultz, MD
Ann Mason, CRA　　から送られてきました…。 どこかに配る？

The International
Pleuropulmonary Blastoma Registry
Children's Hospitals and Clinics of Minnesota
Minneapolis, MN 55404 USA

Pleuropulmonary Blastoma

Introduction
Pleuropulmonary blastoma or PPB is a rare lung tumor, most common in children under the age of 7 years. There are 4 types of PPB. Type I PPB is an air filled cyst which contains a layer of malignant (cancerous) cells. These cells can grow quickly and sometimes Type I PPB can progress to Type II or Type III. Type II PPB has both cystic and solid components and Type III PPB is a solid and often very large tumor within the chest. Type I PPB does not always progress and in some cases the quickly-growing cells may go away (or "regress") leading to a thin walled cyst, which is called Type Ir or Type I PPB with regression.

Presentation
Type I PPB is most commonly diagnosed in children under the age of 1 year. Type II PPB is diagnosed at an average age of 3 years. Type III PPB is diagnosed at an average age of 3.5 years, usually under age 7 years. Type Ir PPB may be diagnosed at any age and may be found incidentally when a CT scan is done for another reason. Individuals with PPB may have difficulty breathing, collapsed lung (pneumothorax), fevers or difficulty gaining weight or may be initially thought to have pneumonia.

Treatment
Type I PPB is treated with surgery. Chemotherapy may be needed for some individuals with Type I PPB, depending on specific circumstances. Types II and III PPB require surgery with chemotherapy and often radiation therapy. Type I PPB is usually only found in the lung. Types II and III PPB may spread to other areas of the body and imaging studies of multiple areas of the body are usually done to determine if the PPB has spread. For all children with PPB, medical exams and imaging are done on a scheduled basis after the PPB is removed. The exact timing of of these exams is determined by the type of PPB and other circumstances.

Genetics
Many children with PPB have a change in a gene called *DICER1* that makes the gene not work properly. When this gene is not working properly, tumors are more likely to occur. Other benign (not cancer) or malignant tumors that may be seen in individuals with *DICER1* mutations include a benign kidney tumor called cystic nephroma, another kidney tumor called Wilms tumor, thyroid nodules or goiter or thyroid cancer, ovarian tumors, and, very rarely, certain childhood brain tumors including pituitary blastoma and pineoblastoma. While some individuals with *DICER1* changes develop one or more tumors or have findings such as lung cysts of thyroid nodules, many are healthy throughout their lifetime.

When a child or adult is diagnosed with one of the conditions above, genetic testing can determine if a *DICER1* change is present. If a *DICER1* change is found, *DICER1* testing may be recommended for family members. Screening for other *DICER1*-related conditions is

recommended for those who do have the change in their *DICER1* gene so that if a tumor arises, it can be found early, when it's most treatable.

For more information:
The International Pleuropulmonary Blastoma Registry was established at Children's Minnesota in 1988 to study PPB and other related conditions. The Registry has enrolled children from 43 U.S. states and 49 countries and serves as a resource for health care providers, patients and families. For more information visit www.PPBregistry.org or email PPBinfo@childrensMN.org