Title: *DICER1*-Related Disorders *GeneReview* - Supplemental Material: Molecular Genetic Pathogenesis of *DICER1*-Related Disorders

Authors: Doros L, Schultz KA, Stewart DR, Bauer AJ, William G, Rossi CT, Carr A, Yang J, Dehner LP, Messinger Y, Hill DA

Date: April 2014

Note: The following information is provided by the authors listed above and has been reviewed by *GeneReviews* staff.

Molecular Genetic Pathogenesis of *DICER1*-Related Disorders

Through the study of pleuropulmonary blastoma (PPB), it became clear that PPB was part of a familial tumor susceptibility syndrome. This led to a linkage study that identified mutation of *DICER1* as the main genetic cause of risk for PPB and related tumors [Hill et al 2009].

Pleuropulmonary blastoma (PPB). The architecture of PPB early in development is a multilocular cyst within the lung parenchyma (type I PPB). The cyst walls are lined by benign-appearing alveolar-type epithelium. The cyst walls contain variable numbers of primitive mesenchymal cells, some of which show differentiation along either skeletal muscle or cartilaginous lines.

Preliminary data from PPB mouse models and study of human tumors suggests that the DICER1 protein is diminished in lung epithelium overlying the mesenchymal tumor suggesting that loss of miRNAs in developing lung epithelium may affect regulation of secreted growth factors driving mesenchymal proliferation and setting the stage for cancerous transformation. In later stages of tumorigenesis, the primitive mesenchymal cells within the cyst wall expand and overgrow the epithelial cysts forming an overtly malignant cystic and solid (type II) or purely solid (type III) sarcoma.

This mesenchymal transformation seems to begin with somatic missense *DICER1* pathogenic variants in tumor cells confirming that *DICER1* is a two-hit tumor suppressor [de Kock et al 2013; Pugh et al, in press]. Specific somatic pathogenic variants in one allele coupled with loss of the other allele leads to defective production of miRNAs from the 5' (5p) end of the miRNA hairpin of the precursor miRNA [Gurtan et al 2012; Anglesio et al 2013; Pugh et al, in press]. These 5p miRNAs, including the let7 family, are important in controlling proliferation and differentiation in development. p53 loss with or without mutation of *TP53* is frequently seen with tumor progression [Pugh et al, in press].

Not all type I PPB are destined to progress to type II and then type III PPB. Multiple older children and adults with a *DICER1* germline pathogenic variant have benign lung cysts. Histologic review of these cysts demonstrated the unique cystic architecture of the type I PPB but lacking the primitive mesenchymal cells [Hill et al 2008].

Cystic nephroma (CN). The architecture and pathogenesis of CN appears to mimic that of type I PPB presenting with epithelial lined cysts in loose mesenchyme. The same

somatic missense *DICER1* pathogenic variants seen in type I PPB are also seen in CN. The cystic pathology is recapitulated in mouse models of *DICER1* ablation in ureteric bud epithelium. There appears to be a low risk of malignant transformation in CN with a sarcomatous tumor morphology similar to solid-type PPB [Doros et al 2014].

Multinodular goiter (MNG) of the thyroid gland in the setting of a *DICER1* germline pathogenic variant shows alteration in miRNA expression but the contribution to the phenotype is not known for certain.

Botryoid-type embryonal rhabdomyosarcoma (ERMS) and **nasal chondromesenchymal hamartoma (NCMH)** show a similar relationship between mesenchyme and epithelium in the early stages and likely have a similar pathogenesis to PPB and CN [Dehner et al 2012].

Little is known about the pathogenesis of **ovarian sex cord-stromal tumors, ciliary body medulloepithelioma (CBME)**, **pineoblastoma** or **pituitary blastoma** associated with *DICER1* syndrome.

References

Anglesio MS, Wang Y, Yang W, Senz J, Wan A, Heravi-Moussavi A, Salamanca C, Maines-Bandiera S, Huntsman DG, Morin GB. Cancer-associated somatic DICER1 hotspot mutations cause defective miRNA processing and reverse-strand expression bias to predominantly mature 3p strands through loss of 5p strand cleavage. J Pathol. 2013;229:400-9.

de Kock L, Plourde F, Carter MT, Hamel N, Srivastava A, Meyn MS, Arseneau J, Bouron-Dal Soglio D, Foulkes WD. Germ-line and somatic DICER1 mutations in a pleuropulmonary blastoma. Pediatr Blood Cancer. 2013;60:2091-2.

Dehner LP, Jarzembowski JA, Hill DA. Embryonal rhabdomyosarcoma of the uterine cervix: a report of 14 cases and a discussion of its unusual clinicopathological associations. Mod Pathol. 2012;25:602-14.

Doros LA, Rossi CT, Yang J, Field A, Williams GM, Messinger Y, Cajaiba MM, Perlman EJ, A Schultz K, Cathro HP, Legallo RD, Lafortune KA, Chikwava KR, Faria P, Geller JI, Dome JS, Mullen EA, Gratias EJ, Dehner LP, Hill DA. DICER1 mutations in childhood cystic nephroma and its relationship to DICER1-renal sarcoma. Mod Pathol. 2014 Jan 31. Epub ahead of print

Gurtan AM, Lu V, Bhutkar A, Sharp PA. In vivo structure-function analysis of human Dicer reveals directional processing of precursor miRNAs. RNA. 2012;18:1116-22.

Hill DA, Ivanovich J, Priest JR, Gurnett CA, Dehner LP, Desruisseau D, Jarzembowski JA, Wikenheiser-Brokamp KA, Suarez BK, Whelan AJ, Williams G, Bracamontes D, Messinger Y, Goodfellow PJ. *DICER1* mutations in familial pleuropulmonary blastoma. Science. 2009;325:965.

Hill DA, Jarzembowski JA, Priest JR, Williams G, Schoettler P, Dehner LP. Type I pleuropulmonary blastoma: pathology and biology study of 51 cases from the international pleuropulmonary blastoma registry. Am J Surg Pathol. 2008;32:282-95.

Pugh TJ, Yu W, Yang J, et al. Exome sequencing of pleuropulmonary blastoma reveals frequent biallelic loss of TP53 and two-hits in DICER1 resulting in retention of 5p-derived miRNA hairpin loop sequences. Oncogene. In press.