

TSC2/TSC1 Field:

Am J Respir Crit Care Med. 2013 Mar 15;187(6):663-5.

Exonic Mutations of TSC2/TSC1 Are Common but Not Seen in All Sporadic Pulmonary Lymphangiomyomatosis.

[Badri KR](#), [Gao L](#), [Hyjek E](#), [Schuger N](#), [Schuger L](#), [Qin W](#), [Chekaluk Y](#), [Kwiatkowski DJ](#), [Zhe X](#).

Main Points covered in the paper

The determination of TSC2 mutations in 10 S-LAM patients that had lung transplant was determined by using a micro-dissection (LCM) and next-generation sequencing (NGS) protocol to isolate the lesions LCM was performed on frozen sections to collect LAM cells from nodules and avoid inclusion of lymphatic channels, lymphocytes, and other cell types. The authors reported a high read depth in the coding region of TSC2. They observed nine different pathogenic sequence variants in eight different sporadic LAM samples, ranging from 4 to 60% rate

What is the relevance of the study?

The occurrence of TSC2 mutations at relatively low frequency or no defects at all in these LAM samples poses an important question. Is a genetic effect in TSC2 the main driving force in the genesis or progression of S-LAM? As the authors of the report said, it is possible that TSC2 mutations occur in a subset of LAM cells and suggest that alternative genetic mechanisms may be operative in some cases of LAM.

Is there a public health implication of the research described in this paper?

As it has been reported previously, it has been determined that Sirolimus therapy was an effective therapy for treatment of LAM. This drug blocks the pathway that is aberrant in those cells lacking functional TSC2. However, it is notable that continuing FEV1 decline was seen in 50% of patients on drug therapy. It is possible, then, that some of these non-responders do not have loss of TSC2 functions and suggest that a full genome sequencing of these patients samples might be warranted.

LAM or TSC Disease Models:

Am J Respir Cell Mol Biol. 2013 Mar 22. [Epub ahead of print]

Faslodex Inhibits Estradiol-induced ECM Dynamics and Lung Metastasis in a Model of LAM.

Li C, Zhou X, Sun Y, Zhang E, Mancini JD, Parkhitko A, Morrison TA, Silverman EK, Henske EP, Yu JJ.

Source: Brigham and Women's Hospital and Harvard Medical School, Boston, United States.

Main Points covered in the paper

Lymphangiomyomatosis (LAM) has been associated TSC2 mutations and in a model of the disease it was shown that estradiol increases the metastasis of TSC2-deficient cells in mice carrying xenograft tumors. In this report, the activity of an anti-estradiol drug (faslodex) was tested to determine whether this approach might be further developed to humans. The results showed that Faslodex normalized the type IV collagen changes in xenograft tumors, enhanced the survival of the mice, and completely blocked lung metastases.

What is the relevance of the study?

An unanswered question in the genesis/progression of LAM is the exact role that estrogens play. The data presented in this study, albeit in an animal model of the disease, showed that Faslodex inhibits the estradiol-induced lung metastasis of TSC2-deficient cells and suggest that targeting estrogen receptors with Faslodex may have efficacy in the treatment of LAM.

Is there a public health implication of the research described in this paper?

It could be an important observation that will require a clinical validation in actual patients.

Clinical Studies:

J Bras Pneumol. 2013 Feb;39(1):5-15.

Doxycycline use in patients with Lymphangiomyomatosis: biomarkers and pulmonary function response.

[Article in English, Portuguese]

Pimenta SP, Baldi BG, Kairalla RA, Carvalho CR.

Hospital A. C. Camargo, São Paulo, SP, Brasil.

Main Points covered in the paper

The data described in this paper is a follow up to a previous report from the same authors. The main trust of the study was To assess whether blockade of matrix metalloproteinase (mainly MMP-2 and MMP-9,) with doxycycline results in changes in pulmonary function

(FEV1), in patients with Lymphangiomyomatosis (LAM) during a 12 months period.

What is the relevance of the study?

It has been proposed that a key role in the destruction of the lung tissue seen in LAM patients is played by the imbalance in the activity of matrix remodeling enzymes such as the metalloproteinases. Therefore, establishing whether a reduction in their activity and/or expression would result in therapeutic response is a critical aspect of the study. The fact that the authors showed that treatment of patients with LAM with doxycycline treatment results in effective MMP blockade along with modest improvement in lung function and quality of life in those with less severe disease, offers a hope that a well controlled study might be worth the efforts to be pursued.

Is there a public health implication of the research described in this paper?

Unfortunately no. The data showed that the benefits seen in the patients did not seem to be related to the MMP changes suggesting that the activity associated with the drug might be due to a different mechanism. (Brazilian Registry of Clinical Trials - ReBEC; identification number RBR-6g8yz9 [<http://www.ensaiosclinicos.gov.br>]).

Chest. 2013. doi:10.1378/chest.122813

Lymphangiomyomatosis Screening in Women with Tuberous Sclerosis

Corey J. Cudzilo; Rhonda D. Szczesniak; Alan S. Brody; Mantosh Rattan; Darcy A. Krueger; John J. Bissler; David N. Franz; Francis X. McCormack; Lisa R. Young

Main Points covered in the paper

The authors set out develop a CT screening to aid in the early detection of LAM in TSC patients.

What is the relevance of the study?

Since Lymphangiomyomatosis (LAM) occurs in at least 40% of women with Tuberous Sclerosis Complex (TSC), an early identification of the disease might have an important role in informing life style choices and treatment decisions. It was found the risk of LAM was age-dependent, rising by about 8% per year. The prevalence of LAM was 27% in subjects <21 years and 81% in subjects >40 years. Among asymptomatic subjects with LAM, 84% had cysts present in the single image at level of the carina. Most subjects with LAM eventually developed pulmonary symptoms (63%), and 12.5% died due to LAM.

Is there a public health implication of the research described in this paper?

These results suggest that most women with TSC ultimately develop cystic changes consistent with LAM, and that most cases can be identified from a single CT slice at the level of the carina. The authors suggest that an age-based approach using limited CT scanning methods may facilitate screening and subsequent treatment decisions with decreased radiation exposure in this at-risk population.

Newsworthy:

[Jacksonville woman awaits double lung transplant](#)