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LAM in the News
June 2013

TSC2/TSC1 Field:

J Comp Neurol. 2013 Jun 8. doi: 10.1002/cne.23380. [Epub ahead of print]
A comparative analysis of Tsc1 and Tsc2 single and double radial glial cell mutants.
Mietzsch U, McKenna J 3rd, Reith RM, Way SW, Gambello MJ.

Main points covered in the paper

Tuberous sclerosis complex (TSC) is a neurodevelopmental disorder with variable phenotypic impact. The relevance of specific mutations in either of two genes, TSC1 (hamartin) or TSC2 (tuberin) is, however, yet to be established. Some Genotype-phenotype studies suggest that TSC2 mutations are associated with a more severe neurologic phenotype. The authors set out to compare and contrast the brain phenotypes of Tsc1 and Tsc2 single and double mutants in mice.

What is the relevance of the study?

The methodology used in this study allowed the authors to establish the effect of gene deletions in specific neuro-derived cells. Thus, the Tsc1 and/or Tsc2 gene were deleted in radial glial progenitor cells. The results showed that mutants of either gene had remarkably similar phenotypes (early postnatal mortality, brain overgrowth, laminar disruption, astrogliosis, a paucity of oligodendroglia, and myelination defects) although double Tsc1/ Tsc2 mutants died earlier than single mutants. Interestingly, single mutants showed differences in the location of heterotopias and the organization of the hippocampal stratum pyramidale suggesting that specific neurological impact might be achieved.

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

The current efforts to map all the gene defects associated with specific diseases and correlate those changes with pathological impact is one of the main goals of translational medicine. Thus, in the case of TSC the data provides further genetic evidence for individual hamartin and tuberin function that may explain some of the genotype-phenotype differences seen in the human disease.

LAM or TSC Disease Models:

Dis Model Mech. 2013 Jun 5. [Epub ahead of print]
Tuberous Sclerosis Complex neuropathology in mouse models is affected by the timing of mutation rather than by mutation in Tsc1 or Tsc2 genes.

Magri L, Cominelli M, Cambiaghi M, Cursi M, Leocani L, Minicucci F, Poliani PL, Galli R

Main points covered in the paper

As it was mentioned in the previous section, a significant genotype-phenotype correlation in patients bearing mutations in TSC1 and TSC2 has not been firmly established, although there is a consensus that TSC2 associated defects are more severe. In this study, it is reported that loss of Tsc1 expression in undifferentiated radial glia cells (RGCs) early during development yields the same phenotype detected upon deletion of Tsc2 in the same cells.

What is the relevance of the study?

The mouse model described in this paper allows the authors to establish an important fact; deletion of either Tsc1 or Tsc2 gene induces mostly overlapping phenotypic neuro-pathological features when performed early during neurogenesis.

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

Not directly but in the future it might allow to classify the patient population accordingly to the embryonic state upon where the defects first took place.

Clinical Studies:

The Lancet Respiratory Medicine, Early Online Publication, 20 June 2013
doi:10.1016/S2213-2600(13)70090-0

Serum VEGF-D concentration as a biomarker of lymphangioleiomyomatosis severity and treatment response: a prospective analysis of the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial

Dr Lisa R Young MD, Hye-Seung Lee PhD, Yoshikazu Inoue MD, Joel Moss MD, Lianne G Singer MD, Prof Charlie Strange MD, Prof Koh Nakata MD, Prof Alan F Barker MD, Jeffrey T Chapman MD, Prof Mark L Brantly MD, Prof James M Stocks MD, Prof Kevin K Brown MD, Prof Joseph P Lynch MD, Hilary J Goldberg MD, Prof Gregory P Downey MD, Jeffrey J Swigris DO, Angelo M Taveira-DaSilva MD, Prof Jeffrey P Krischer PhD, Prof Bruce C Trapnell MD, Prof Francis X McCormack MD, for the MILES Trial Group

Main points covered in the paper

The issue of finding a "bio-marker" for LAM (either as a diagnostic , prognostic and or treatment response) has been a challenge not fully met. The authors describe the use of VEGF-D as a potential circulating marker for LAM taking advantage of the clinical trial data collected during the sirolimus clinical trial.

What is the relevance of the study?

Serum VEGF-D concentrations were measured at three points during the treatment period (baseline, 6 and 12 months). The results were analyzed to establish a correlation between the VEGF-D concentrations and clinical, physiological, and patient-reported outcomes.

Although the results are encouraging, a significant number of patients that responded to treatment with a reduction in the VEGF-D values showed a minor response in their lung function. Thus, improvement in baseline-to-12-month FEV_1 occurred in 15 of 23 (65%) of patients that modulated their VEGF-D levels. On the other hand, there was a noticeable number of patients that showed clinical response and yet did not changed their VEGF-D in response to treatment.

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

Absolutely. However, its value will require a further refinement of the correlation between the serum biomarker (VEGF-D) and the clinical outcome.

Clinical Utility Gene Card:

European Journal of Human Genetics advance online publication 12 June 2013; doi: 10.1038/ejhg.2013.129

Clinical utility gene card for: Tuberous sclerosis complex (TSC1, TSC2)

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http://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg2013129a.html

The article published by this journal is a very useful resource that summarizes many key features of the TSC disease from genetic to diagnostics approaches.

Newsworthy:

The following announcement (June 19, 2013) was made by the BioNewsTexas regarding a grant received by the Baylor College of Medicine

(http://bionews-tx.com/?s=eissa)

The National Institutes of Health's (NIH) *Discovering New Therapeutic Uses for Existing Molecules Program* has just awarded Dr. N. Tony Eissa (professor of medicine in the section of pulmonary, critical care and sleep medicine) at Baylor College of Medicine in Houston a grant for $1.3 million to explore a new treatment for lymphangioleiomyomatosis (LAM). Another $3 million is expected after the first year as various goals have been achieved.

Eissa will be studying AstraZeneca's Src/Abl kinase inhibitor known as saracatinib. He will determine if the drug is safe and has the ability to decrease growth and spread of LAM cells in mice. If successful, Eissa and colleagues will conduct multi-center clinical trails on patients who have LAM.

According to Eissa, "Although the origin of LAM cells is unknown, it is clear that they migrate to the lungs from somewhere else in the body. The proposed new treatment will try to reduce the growth, mobility and invasiveness of LAM cells. This work is being tested in cells at the bench and in mice before moving to humans."

Collaborating investigators that will join in include Drs. A. Tyryshkin and N. Hanania of Baylor College of Medicine, Dr. F McCormack of the University of Cincinnati, Dr. Hhalid Almoosa of the University of Texas Health Science Center at Houston, Dr. D. Dilling of Loyola University of Chicago and Dr. S. Ruoss of Stanford University. Drs. Hye-Seung Lee and J. Krischer from the University of South Florida will act as the Data Coordinating Center for this research.