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| 学位論文の題名 | A combination of genetic and biochemical analyses for the diagnosis of PI3K-AKT-mTOR pathway-associated megalencephaly<br>(PI3K-AKT-mTOR 経路の異常により起こる巨脳症の遺伝学的、生化学的診断法)<br><br>BMC Medical Genetics 2017; 18(1): 4 |
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**Abstract**

**Background:** Constitutive activation of the PI3K-AKT-mTOR pathway (mTOR pathway) underlies megalencephaly in many patients. Yet, prevalence of the involvement of the PI3K-AKT-mTOR pathway in patients with megalencephaly remains to be elucidated, and molecular diagnosis is challenging. Elucidation of the molecular mechanisms underlying megalencephaly is crucial to determine the value of investigating therapeutic agents, such as rapamycin, in the context of mTOR pathway-associated megalencephaly. Here, we have successfully established a combination of genetic and biochemical methods for diagnosis of mTOR pathway-associated megalencephaly, and have attempted to delineate the clinical characteristics of the disorder.

**Methods:** Thirteen patients with an increased head circumference and neurological symptoms participated in the study. To evaluate the activation of the mTOR pathway, we performed western blot analysis to determine the expression levels of phosphorylated S6 ribosomal protein (phospho-S6 protein) in lymphoblastoid cell lines from nine patients. Multiplex targeted sequencing analysis for 15 genes involved in the mTOR pathway was performed on 12 patients, and whole-exome sequencing was performed on one additional patient. Clinical features and MRI findings were also investigated.

**Results:** We identified pathogenic mutations in six (*AKT3*, 1 patient; *PIK3R2*, 2 patients; *PTEN*, 3 patients) of the 13 patients. Increased expression of phospho-S6 protein was demonstrated in all five

mutation-positive patients in whom western blotting was performed, as well as in three mutation-negative patients. Developmental delay, dysmorphic facial features were observed in almost all patients. Syndactyly/polydactyly and capillary malformations were not observed, even in patients with *AKT3* or *PIK3R2* mutations. There were no common phenotypes or MRI findings among these patients.

**Conclusions:** A combination of genetic and biochemical methods successfully identified mTOR pathway involvement in nine of 13 (approximately 70%) patients with megalencephaly, indicating a major contribution of the pathway to the pathogenesis of megalencephaly. Our study also disclosed the surprisingly broad clinical spectrum of the mTOR pathway associated megalencephaly. Our combined approach could be useful to identify patients who are suitable for future clinical trials using an mTOR inhibitor.