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SEIZURES AND BRAIN MALFORMATIONS IN MODEL MICE FOR GLYCINE ENCEPHALOPATHY

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Glycine encephalopathy (nonketotic hyperglycinemia) is caused by defect in the glycine cleavage system (GCS), and characterized by severe neurological symptoms such as coma and intractable seizures in neonates. Examinations by CT and MRI scans have revealed unexpectedly high association of brain malformation with glycine encephalopathy. To elucidate the neuropathogenesis we generated model mice for glycine encephalopathy using transgenic expression of a dominant-negative glycine decarboxylase. Conditional expression by the Cre-loxP system enabled us to induce the dominant-negative mutant enzyme specifically in the offspring. Seizures developed in all the model mice within two days of life, which resulted in fatal status epileptics. The pups presented marked microcephaly associated with cerebellar hypogenesis. These phenotypes were similar with those observed in patients with glycine encephalopathy. Histological examination revealed reduced number of the neurons in various areas of the central nervous system, especially in cerebral cortex and basal ganglia. These results suggest a pivotal role of the GCS in developing brain.

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HIGH FREQUENCY OF CARRIERS WITH SLC25A13 MUTATIONS IN EAST ASIA

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Citrin encoded by SLC25A13 gene, an aspartate glutamate carrier, is an essential component of the malate aspartate shuttle and urea synthesis. Citrin deficiency causes adult-onset type II citrullinemia (CTLN2) and neonatal hepatitis with intrahepatic cholestasis (NICCD). It has been thought to be restricted to Japan, but very recently some cases have been found in the other countries (4 Chinese patients, three from Taiwan and one from China, a Vietnamese in Australia, a Palestinian and an Ashkenazi Jewish in Israel), indicating a wide distribution of citrin deficiency among races. DNA diagnosis of nine mutations identified in Japanese CTLN2 and NICCD patients has revealed that the carrier frequency is 1/69 in the Japanese population. In this preliminary study, we detected a similar frequency in China (1/79), Taiwan (1/98) and Korea (1/50) but not in Caucasian, suggesting that many CTLN2 and NICCD patients exist in East Asia.

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Frequency of heterozygote with the mutated SLC25A13 gene in East Asia

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東アジア諸国におけるSLC25A13変異遺伝子の頻度検索

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[はじめに] 我々は成人発症 II 型シトルリン血症 (CTLN2) の責任遺伝子として SLC25A13 を発見し、その遺伝子産物を citrin と命名した [1]。SLC25A13 変異同定と遺伝子診断法確立 [1-3]は、CTLN2 の新生児期症状、胆汁うっ滞新生児肝炎 (NICCD) の発見に繋がった [4-7]。また、citrin の機能 (mitochondrial aspartate glutamate carrier) 解明 [8]により、NICCD や CTLN2 の多彩な病態発症および適応機構に対する推察 [9]も可能になってきた。さらに、本邦の一般集団の解析から、70 人に 1 人の割合で保因者が存在することを見いだし、SLC25A13 変異遺伝子ホモ接合体頻度が高い (1/20,000) ことを明らかにした [1-3,9]。Citrin 欠損症は日本に特有の疾患と思われていたが、我々はこれまでに、中国人 CTLN2 症例 [10]、ベトナム人 NICCD 症例、パレスチナ人 NICCD 症例においても SLC25A13 変異を見いだしてきた。そこで今回、東アジアにおける変異遺伝子頻度を検索したので、報告する。

[対象と方法] 韓国、台湾、中国に由来する東アジア人の乾燥濾紙血から DNA を抽出し、主に GeneScan/SNaPshot 法 [3]を用いた遺伝子診断法により、9 種類の既知変異 ([I]851del4, [II]IVS11+1G>A, [III]1638ins23,[IV]S225X, [V]IVS13+1G>A, [VI]1800ins1, [VII]R605X, [VIII]E601X, [IX]E601K) に対する検索を行なった。

[結果と考察] 今回の解析によって得られた保因者頻度は、韓国：50 人に 1 人、台湾：130 人に 1 人、中国：78 人に 1 人の割合であり、日本とほぼ同じレベルを示した。保因者が持つ変異を比較すると、日本の場合 (70 人に 1 人) [2,3,9]、変異[I]: 4, [II]: 9, [III]: 1, [IV]: 5, [V]: 1 人と、変異[II]が多いのに対して、韓国では[I]: 2, [II]: 1, [VII]: 1 人、台湾では[I]: 2, [III]: 1 人、中国では[I]: 5 人と、変異[I]が多かった。これは、共同研究によって実施した CTLN2 症例の診断結果、台湾の 2 例は[I]/[I]と[I]/[III][10]、中国の 1 例は[I]/[III] (Yang et al. unpublished data)、を反映していた。以上のことは、東アジアにおいて SLC25A13 変異が広く分布していることを示唆する。

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