科技部新聞稿

破解前三大過敏藥物-抗癲癇藥 Phenytoin 過敏基因之謎

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嚴重致命的藥物過敏反應

吃藥可救命也可能會致命！大部分的人吃藥都不會有副作，但少部分特殊體質的人卻會引起嚴重致命的過敏反應。輕者皮膚紅疹，嚴重者會造成肝、腎衰竭甚至引起像燒燙傷一樣致命的皮膚黏膜潰爛，例如「史帝文生強生症候群」或「毒性表皮溶解症」等。

常見引起嚴重皮膚藥物過敏反應藥物及基因謎團

台灣藥害救濟的三大常見藥物是降尿酸藥物-安樂普利諾(allopurinol)，及抗癲癇藥物-癲能停(phenytoin)、卡巴氮平(carbamazepine)，佔近十年來台灣藥害救濟五成以上的案例，這三個藥也是全球藥害的三大”惡首”。

過去台灣藥物過敏研究團隊已解開了全球常見過敏藥物-降尿酸藥(安樂普利諾; allopurinol)及卡巴氮平(carbamazepine) 之過敏基因，發現是免疫基因--人類白血球抗原 HLA-B*1502, HLA-B*5801。目前這些基因發現已廣泛應用於國內與國外的臨床篩檢。雖然，安樂普利諾與卡巴氮平的藥物過敏已經找的避免的方法了，但目前排行第二的”惡首”過敏藥物-癲能停(phenytoin)的基因謎團全球的科學家遲遲無法破解，雖然癲能停(phenytoin)和卡巴氮平(carbamazepine)藥物結構類似，但此藥過敏體質的病患和人類白血球抗原 HLA-B*1502 的關係很弱，無法篩檢預防，目前仍很多人遭受此藥物過敏甚至致命之傷害！

目前唯一有適應症預防腦部手術後癲癇發作的藥物-癲能停 Phenytoin

癲能停 Phenytoin 是第一線抗「癲癇」的老藥，由於是目前唯一有適應症預防腦部手術後癲癇發作的藥物，因此全球每年有數百萬人需要接受此藥的治療。台灣一年約有 4 萬人新使用者會接受此藥物治療，其中約 1%的人會引起過敏反應，嚴重者會

引起致命的「史帝文生強生症候群」或「毒性表皮溶解症」，過去長庚醫院 6 年就有 8 名此藥引起的死亡案例，台灣藥害救濟過去 12 年就有 108 件此藥的藥害救濟！前陣子新聞報導知名歌手江蕙攝影師的母親開刀，產生嚴重致命的過敏反應就是使用此藥！

台灣研究團隊再次領先全球、解開癲能停(phenytoin)藥物過敏基因之謎-榮登「美國醫學會雜誌 JAMA」

由科技部補助--長庚醫院與陽明大學的跨國藥物過敏研究團隊，再次領先全球、破解癲能停 Phenytoin 引起嚴重藥物過敏基因之謎，榮登「美國醫學雜誌 JAMA」。加上前兩個藥物過敏基因之發現，全球前三大佔五成以上之嚴重皮膚藥物過敏案例的基因謎團，都被本研究團隊成功地破解。此重大成果的發表，見證了台灣於藥物過敏研究領先全球的地位。

顛覆主流觀念，首次揭發"代謝不好"的體質基因和藥物過敏有強烈關聯

本研究發現癲能停 (phenytoin)之過敏基因並非以往常見和藥物過敏相關的人類白血球抗原，此神秘基因並非免疫基因，而是和藥物代謝途徑有關之基因--細胞色素 P450(Cytochrome P450)簡稱 CYP。此發現顛覆了現今科學家對引發藥物過敏之主流--免疫基因之觀念，首次揭發”代謝不好”的體質和藥物過敏也有**強烈關聯**！若是屬代謝不好的 CYP 基因型，服用癲能停後會代謝不良，因發後續之過敏免疫反應。由於癲能停(phenytoin)和安樂普利諾(allopurinol)及卡巴氮平(carbamazepine)是全球引起嚴重致命藥物過敏的三大常見藥物(佔五成以上)，台灣藥物過敏研究團隊這十年來連續破解了這三大”惡首”藥物之過敏基因，未來可應用於預防全球超過一半的嚴重藥物過敏悲劇之發生！因此，此成果格外受國際頂尖醫學期刊重視。此”代謝不好”和藥物過敏反應有關的新發現，將可應用於研究目前上百種仍未知相關過敏基因之藥物，加速了「個人化醫療」時代的到來！

台灣為首研究團隊，領導全球

本研究發現不僅適用於台灣病患，日本衛生研究院(NIH)，中國大陸及東南亞國

家的研究單位也應邀加入本研究，證實有相同的結果。因此，此研究發現未來將會應用於亞洲及全球臨床上開立此藥物前的過敏基因篩檢。此研究成果於 8 月 5 日(台灣時間 8 月 6 日)刊登於頂尖的醫學期刊-美國醫學會雜誌（JAMA）。

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附件

Study Identifies Genetic Variants Associated with Severe Skin Reactions to Commonly Used Antiepileptic Drug

Researchers have identified genetic variants that are associated with severe adverse skin reactions to the antiepileptic drug phenytoin, according to a study in the August 6 issue of *JAMA.*

Phenytoin is a widely prescribed antiepileptic drug and remains the most frequently used first-line antiepileptic drug in hospitalized patients. Although effective for treating neurological diseases, phenytoin can cause cutaneous (skin) adverse reactions ranging from mild to severe. The pharmacogenomic basis of phenytoin-related severe cutaneous adverse reactions has not been known, according to background information in the article.

Wen-Hung Chung, M.D., Ph.D., of Chang Gung Memorial Hospital, Keelung, Taiwan, and colleagues investigated the genetic factors associated with phenytoin-related severe cutaneous adverse reactions. The case-control study was conducted in 2002-2014 among 105 cases with phenytoin-related severe cutaneous adverse reactions (n=61 Stevens-Johnson syndrome/toxic epidermal necrolysis and n=44 drug reactions with eosinophilia and systemic symptoms), 78 cases with maculopapular exanthema (a less severe type of rash), 130 phenytoin-tolerant control participants, and 3,655 population controls from Taiwan, Japan, and Malaysia. A genome-wide association study (GWAS) was conducted using the samples from Taiwan. The initial GWAS included samples of 60 cases with phenytoin-related severe cutaneous adverse reactions and 412 population controls from Taiwan.

Analysis of the data indicated that variants of the gene *CYP2C*, including *CYP2C9*3*, were associated with phenytoin-related severe cutaneous adverse reactions. The statistically significant association between *CYP2C9*3*, known to reduce drug clearance (the elimination of a drug from the body), and phenytoin-related severe cutaneous adverse

reactions was replicated by the samples from Taiwan, Japan, and Malaysia, with a meta-analysis showing an 11 times higher odds of experiencing this reaction with this variant. Delayed clearance of plasma phenytoin was detected in patients with severe cutaneous adverse reactions, especially *CYP2C9*3* carriers, providing a clinical link of the associated variants to the disease.

Delayed clearance was also noted in patients with severe cutaneous adverse reactions without *CYP2C9*3*, suggesting that nongenetic factors such as renal insufficiency, hepatic dysfunction, and concurrent use of substances that compete or inhibit the enzymes may also affect phenytoin metabolism and contribute to severe cutaneous adverse reactions.

"This study identified *CYP2C* variants, including *CYP2C9*3*, known to reduce drug clearance, as important genetic factors associated with phenytoin-related severe cutaneous adverse reactions. These findings may have potential to improve the safety profile of phenytoin in clinical practice and offer the possibility of prospective testing for preventing phenytoin-related severe cutaneous adverse reactions. More research is required to replicate the genetic association in different populations and to determine the test characteristics and clinical utility," the authors conclude.

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