行政院國家科學委員會補助專題研究計畫成果報告

****

* 臺灣愛滋病毒亞型對治療成果及抗藥性突變之影響 *

****

計畫類別:個別型計畫

計畫編號: NSC-89-2314-B-002-114

執行期間: 88-08-01 to 89-07-31

計畫主持人: 陳 茂 源 陳茂源

執行單位:臺大醫學院

31 October 2000

摘要: 臺灣流行之愛滋病毒亞型主要為 B 及 E 亞型.其比例約為 4 比 1.我們在研究治療愛滋病毒感染但卻引起抗藥性突變病毒的基因變化時,發現 1.產生抗藥性之病毒如預期均有數個主要突變 2.次要突變之數目與抗藥性可能有極大關係 3.是否為次要突變需與用藥前之基因對照 4.亞型特殊之基因變化可能與抗藥性相關. 以上論點之確立有待將來更多資料之收集.

Abstract : The two major HIV 1 subtypes circulating in Taiwan are subtype B and E with a ratio of 4:1. We found that there was different background polymorphism in reverse transcriptase (RT) gene between B and E. By comparing the background and mutated RT and protease genes, we noted that the existence of primary mutations and the number of primary and secondary mutations might be important for the interpretation of genotypic drug resistance test. The study of background polymorphism is required to identify secondary mutations or the pre-existing primary mutations. The contribution of subtype-specific polymorphism to drug resistance requires further study.

Background: Treating HIV-1 infection with highly active anti-retroviral treatment (HAART) had met with great success in the beginning. However, a substantial proportion of patients treated for HIV-1 infection experienced virological failure later [1]. Continuing use of the failed regimen may result in the development of cross-resistance within drug class [2]. Therefore, the knowledge of existing drug resistance mutations will help clinicians to choose the effective salvage therapy. Indeed, recent study showed that patients failing a protease inhibitor based-regimen had achieved greater viral load reduction by using drug resistance genotypic testing [3]. HIV-1 epidemic study in Taiwan showed that the prevailing HIV-1 subtypes are subtype B and E [4]. However, most of the existing drug resistance data were derived from patients infected with subtype B. Moreover, the interpretation of genotypic testing is difficult and no golden rules are available. In the present study, we tried to find and interpret drug resistance mutations among our patients with virological failure and focused on the difference in mutation site between subtype B and E.

Results: The drug resistance mutations in reverse transcriptase (RT) and protease (P) genes of three patients before treatment and when the patients failed antiretroviral treatment were listed below. The primary mutation sites were shown on the top of each table.

Table I. Mutations in protease gene noted in three patients. Primary mutation site are 30D, 46M, 48G, 54I, 82V, 84I and 90L The other mutation sites are secondary mutations.

	46M	84I	90L	10L	11V	13I	15I	20K	35E	36M	37N	41K	62I	69H	70K	71A	73G	77V	85I	88N	93I
17-05-97					I					I	D		V								
03-12-98	I		M	I			V		D	I	D	R	V				S		V		
07-12-99	I		M	I			V		D	I	D	R	V				S/T				
08-04-97	I		M	I			V										S				
13-04-99	I	V	M	I		V	V	T						R			T				
10-12-99	I	V	M	I		V	V	I						R			T				
08-04-97												R			T			I			L
13-10-99	I		M	I								R	V		T	V		I		K	L

Table II. Mutations in reverse transcriptase gene noted in two patients. Primary mutation sites are 69T,70K, 74L, 151Q, 184M, 215T for NRTIs and 103K, 181Y, 190G for NNRTI. Secondary mutations at 41M, 67D, 210L and 219K are associated with AZT resistance.

	69T	70K	74L	151Q	184M	215T	103K	181Y	190G	41M	67D	210L	219K
08-04-97		R				F	R				N		Q
03-10-99			I		V	F				L	N		Q
13-04-99					V					L	N		
10-12-99					V	F	N			L	N		W

Other secondary mutations

	6E	28E	32K	35V	39T	101K	106V	117S	121D	122E	135I	166K	177D	196G	202I	203E	207Q	208H	214F
08-04-97	K	E	L						N	K	V						E		L
03-10-99	D K		L	A	V		A		N	K	V					K	E	Y	L
13-04-99			I	A		I					T	R	E	E	V			Y	
10-12-99			I	A		I					T	R	E	E	V			Y	

We also found some subtype specific polymorphism in reverse transcriptase gene.

Interestingly, treatment failure was associated with mutations at two of these sites.

Subtype-specific polymorphism

	Position in reverse transcriptase gene						
	6	11	35	43	123	174	177
Subtype B	Glu	Lys	Val	Lys	Asp	Gln	Asp
Subtype E	Asp	Thr	Thr	Glu	Ser	Lys	Glu

Discussion: We had analyzed more than 20 RT and P genes obtained from patients with treatment failure. The present study tried to find out the rule of interpreting the significance of mutation sites. Besides primary mutations that had been proved to confer resistance to NRTIs and PIs, there were many polymorphism in RT and P genes. However, some polymorphism actually existed in background HIV viral genomes before drug treatment. Therefore, the interpretation of secondary drug-resistant mutations should be made only on the ground of pre-treatment polymorphism.

The number of primary and secondary mutation sites is important clue to the existence of drug resistance. We need more data to find out the significance of individual mutations. Finally, the subtype-specific polymorphism is drug resistant secondary mutations or not requires further study.

Self-evaluation of the present project: The analysis of mutations in reverse transcriptase and protease genes in the presence of antiretroviral treatment had been included in several treatment guidelines. However, no golden rule existed for the interpretation of genotypic or phenotypic drug resistance test. We believed that this project is promising in developing the rule of interpreting genotypic drug resistance test. More importantly, we are going to have the data of non-B HIV-1 drug resistance mutations.

Reference

1.Perrin L, Telenti A. HIV treatment failure : testing for HIV resistance in clinical practice. Science 1998, 280: 1871-1873.

2.Palmer S, Shafer RW, Merigan TC. Highly drug-resistant HIV-1 clinical isolates are cross-resistant to many antiretroviral compounds in current clinical development. AIDS 1999, 13: 661-667.

3.Durant J, Clevenberg P, Halfon P et al. Drug resistance genotyping in HIV-1 therapy: the VIRADAPT randomized controlled trial. Lancet 1999, 353:2195.

4.Lee Chun-Nan, Wang Wei-Kung, Fan Wen-Sheng, Twu Shing-Jer, Chen Shou-Chien, Sheng Ming-Ching, Chen Mao-Yuan*. Determination of human immunodeficiency virus type 1 subtypes in Taiwan by *vpu* gene analysis. J Clin Microbiol 2000, 38:2468-2474.