出國報告(開會)

第 10 屆世界生物精神醫學會
心得報告

服務機關：國防醫學院三軍總醫院
姓名職稱：黃三原、三總精神醫學部主任
派赴國家：捷克布拉格
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摘要

100 年 5 月 30 日本人參加在布拉格舉行的第十屆世界生物精神醫學會，本次會議主題最主要探討生物標記及個人化醫學。在生物標記方面，探討三大主題：第一爲腦影像學，對精神疾病診斷與治療之應用；第二針對憂鬱症與精神分裂症患者的神經滋養因子與 cytokine 之變化；第三主要探討基因體學（基因不一致性）與精神疾病之病理變化與疾病發展有何影響。在影像學部份，目前世界研究學者發現憂鬱症患者與精神分裂症患者腦部之邊緣系統皆有退化與縮小之現象。另外，目前世界研究趨勢亦運用腦部退化之現象進一步分析體內免疫機轉變化與神經滋養因子之多寡是否與精神疾病之病程有關聯。在免疫學與腦部滋養因子之研究部分，雖諸多研究發現腦部滋養因子（BDNF、GDNF）皆可以調整腦神經的再生，進而減少憂鬱或精神分裂症的發生。但此僅爲初步發現，仍需更多學者參與及加入才能得到基因研究一致性的發現。在基因體學部份，雖研究已達二十多年，且有幾個標記基因與憂鬱症或精神分裂症的發生有關；但精神疾病爲複雜性高、差異性大之疾病，單一基因的不一致性仍無法足夠佐證此基因與憂鬱症或精神分裂症有關。

雖目前世界上針對生物標記在精神疾病之診斷、預防性治療及療效預後有很大之期待，但目前仍無一致性的定論，且研究方法學與大量樣本的取得與研究仍需極力克服；但深信在世界精神醫學研究學家不斷研發與創新的努力下，我們仍期待會有一致性之精神相關生物標記能協助我們日後在精神疾病之臨床運用、診斷與治療上有所幫助。

目次

摘要

本文

目的 ----------1

過程 ----------1

心得與建議 ----------4

附錄

附錄一 ----------6

附錄二 ----------7

附錄三 ----------8

本文

目的:

本人本次至布拉格參加第十屆世界生物精神醫學會之主要目的是探討生物標記及個人化醫學，並與國外相關學者做分享討論；另一方面則向他人學習目前世界針對精神疾病的影像運用、基因不一致性及基因研究之方法與經驗。

過程：

本人於 100 年 5 月 29 日上午首次踏上捷克布拉格土地，下午到布拉格國際會議中心（會場）報到，並盡可能熟悉不同會議之地點；此次於布拉格舉行的會議爲第十屆世界生物精神醫學會。雖然此次旅程與報到當天明顯孤立一人，但隔日遇到幾位台灣的研究同好（像是成大醫院的楊延光、台北榮總的周元華與白雅美、中國醫藥大學附設醫院的蘇冠賓），有如他鄉遇故知；雖彼此在台灣大家因工作忙碌鮮少遇到，但在國外可以一起研究討論，使本人得到更多的研究啓發與研究思緒。本人於當天晚間參加本次會議的迎賓晚會，迎賓晚會中有捷克衛生部部長、布拉格市市長及本次大會主席全程參加，可見得此次會議在該國得到行政部門的高度重視。音樂是布拉格的精神與靈魂，在晚宴中，最後當然免不了音樂的演奏。這也令我啓發日後本國及本人如何籌辦世界型會議，從中學習到一些思緒，希望日後本人可以靈活運用。

100 年 5 月 30 日爲正式會議的第一天，本人選擇參加幾場會議如歐洲腦部影像大型整合性計劃及腦部血清素機轉等議題做學習，在歐洲腦部影像大型整合性計劃中，歐洲國家花費了十億歐元（約等同於四百五十億台幣）進行五年有關精神疾病之腦部機轉研究。反觀我們國家五年五百億的計畫僅分配給幾個重點發展大學，且還要再細分給醫學院、工學院、理學院、經濟學院、藝術學院、農學院等多個學術單位；所以我們在研究支持與經費取得和應用上面仍有許多思考的空間。另外，在腦部血清素與 glutamatergic 等作用機轉對精神疾病的學術研討會

中，目前普遍皆認爲多巴胺神經傳遞物質是精神病（psychosis）的主要病理機轉；但經過多年臨床研究與經驗告訴我們多巴胺神經傳遞物質應該僅是重要元素，並非完全經由此神經傳遞物質主導精神病之發生。且最近研究中皆證實血清素與 glutamatergic 的作用機轉在腦部神經之交互變化中扮演相當重要的角色，亦左右精神疾病之發生；所以在未來精神疾病之藥物治療與研發上，glutamatergic 與血清素等神經傳遞物質將會是未來的明星議題。

100 年 5 月 31 日本人選擇幾場議題如下：（1）生物標記在精神疾病之應用；（2）躁鬱症憂鬱型之神經生物因子；（3）神經影像學在精神藥物之應用；（4）神經免疫發炎反應在精神分裂症及憂鬱症等病理學之應用。而會議中最令我印象深刻的爲第二場有關躁鬱症憂鬱型之神經生物因子變化，此場演講者爲日本學者 Tadafumi Kato 教授；此場雖然只有短短一小時的教育性演講，卻很清楚的探討了四大主題，且使用清晰地英文有條有理闡述他四大主題的演說。Kato 教授其研究內容，從動物到人體實驗逐一探討有關粒線體（mitochocondria）及內質網（ER）不平衡與功能失調所引發的相關精神疾病。在整場演說中，我學習到 Kato 教授做研究的嚴謹與清晰的研究思緒，令我深感佩服，這幾乎是我五天中所參加的演討會演講中最精采的一場。兩年後的 2013 年世界生物精神醫學會也預計於日本京都會議舉行，經歷這場演講後讓我啓發台灣何時才能舉辦如此大型之會議，且我們的研究水平是否已跟得上人家的步伐。

100 年 6 月 1 日，本人同樣選擇了四場演講參加，如下：（1）腦部滋養因子（BDNF）可以當情緒疾病的生物標記嗎？；（2）基因體學對個人化醫學在精神疾病之貢獻；（3）神經生物機轉與基因不一致性對自殺的影響；（4）精神疾病之生物標記運用。本日所探討的主題都圍繞在生物標記之研究與探討。值得一提的是，目前個人化醫學（personalised medicine）爲一個非常熱門的探討議題，且本人對基因體學與個人化醫學在精神疾病之運用充滿了興趣，非常期待能從中學習到個人化醫學是否能運用在本土精神病患身上。雖有幾個基因不一致性可能會影響藥物療效與副作用之發生，但其結果目前仍無法充份驗證基因體學可以運用在

精神相關疾病之個人化醫學上。

100 年 6 月 2 日本人有三個壁報展示，依序分別爲：

（1）**Dopamine transporter gene play a risk factor in patient with Heroin dependnec?**

（2）**Dopamine transporter gene (DAT1) dose not influence the pathogenesis of major depressive disorder and its personality trait.**

（3）**Serotonin transporter availability and the genetic polymorphism of SLC6A4 dose not associated with major depression and its severity**

(壁報內容詳見於附錄**)**

本人本日針對三個研究主題如血清素轉運體之腦部影像學對本土漢民族憂鬱症患者之運用，多巴胺轉換器基因不一致性對本 土漢民族憂鬱症患者與海洛因依賴發生之關連性研究；與國外學者做討論與分享。雖我們研究中顯示有關多巴胺轉運體基因變異性對漢民族憂鬱症及海洛依成癮患者之基因病理機轉無顯著關聯性發生。但本人和與會的國外學者討論，雖研究結果顯示皆爲無關聯性，但我們研究團隊真實呈現我們的實際研究結果；這點與其他國外學者有不一致性的看法，由此可證明精神疾病（如憂鬱症、躁鬱症、物質濫用等之患者）其爲異質性與變異性非常大，這可能受彼此的文化、種族、與環境等因素所干擾，所以日後我們的研究應針對環境與個人體質與人格特質加以就類別區分，使研究方向更多元、更完整。

心得及建議：

1.政府部門的重視與國家優點的展現

在正式會議前一晚的迎賓晚宴中，本人看到捷克衛生部部長、布拉格市市長及本次大會主席全程出席參加，可見得此次會議在該國得到行政部門的高度重視。在晚宴中，音樂是布拉格的精神與靈魂，最後當然免不了優美音樂的演奏。這也讓我啓發日後本國及本人如何籌辦世界型會議、如何展現自己國家的優勢，從中學習到一些思緒，希望日後本人可以靈活運用；同時，本人建議日後若國內有舉辦如此大型會議，希望能受到政府相關部門之重視。

2.研究經費的不足與爭取

在歐洲腦部影像大型整合性計劃中，歐洲國家花費了十億歐元（約等同於四百五十億台幣）進行五年有關精神疾病之腦部機轉研究。反觀我們國家五年五百億的計畫僅分配給幾個重點發展大學，且還要再細分給各學科部門，經費實在有限；故日後本國之研究發展，應朝向幾個重要議題做整合性之研究發展，方仍與國際學術機構一較長短。

3.日本研究的扎實，值得我們學習

本次會議的幾個演講主題中，最令我印象深刻的莫過於日本學者 Tadafumi Kato 教授演說有關躁鬱症憂鬱型之神經生物因子變化。此場雖然只有短短一小時的教育性演講，卻很清楚的探討了四大主題，且使用清晰地英文有條有理闡述他四大主題的演說。在此演講中，我學習到 Kato 教授做研究的嚴謹與清晰的研究思緒，令我深感佩服。兩年後的 2013 年世界生物精神醫學會也預計於日本京都會議舉行，經歷這場演講後讓我啓發台灣何時才能舉辦如此大型之會議，且我們的研究水平是否已跟得上人家的步伐。我想，唯有培養年輕學者，從基礎研究扎根，確實做好每個研究的環節；一時投機取巧的文章絕非長久之道。

4.個人化醫學的運用

有關個人化醫學（personalised medicine）是一個非常熱門的探討議題，且本

人對基因體學與個人化醫學在精神疾病之運用充滿了興趣，非常期待能從中學習到個人化醫學是否能運用在本土精神病患身上。雖有幾個基因不一致性可能會影響藥物療效與副作用之發生，但其結果目前仍無法充份驗證基因體學可以運用在精神相關疾病之個人化醫學上。我想，日後經由不斷地精進研發與問題的發掘，未來個人化醫學的夢想。

此次會議旅程使我獲益良多，不只是與國外學者學術交流，還有見識到布拉格當地的風俗民情、地方政府對於研究大量投入的人力和資源，這些都是值得我們國家深思的議題。

附錄

附件一

P-25-001

2011 WFSBP in Prague

Dopamine Transporter Gene play a risk factor in Patient with Heroin Dependence ?

San-Yuan Huang[1*]; Yi-Wei Yeh [1]; Chang-Chih Huang [1]; Ru-Band Lu [2];Mei-Chen Shih[1]

[1] Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC

[2] Institute of Behavior Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC

Objective

Much evidence suggests that dysfunction of dopamine transporter-mediated dopamine transmission may be involved in the pathophysiology of substance abuse and dependence. The aim of this study was to examine whether the dopamine transporter gene (*DAT1*; *SLC6A3*) is associated with the development of heroin dependence (HD), and whether *DAT1* influences personality traits in patients with HD.

Methods

Fifteen polymorphisms of *DAT1* were analyzed in a case-control study of 1046 Han Chinese (615 patients and 431 controls). All participants were screened using a Chinese version of the modified Schedule of Affective Disorder and Schizophrenia-Lifetime (SADS-L) and all patients met the DSM IV criteria for HD. Furthermore, a Chinese version of the Tridimensional Personality Questionnaire (TPQ) was used to assess personality traits in the patient group and examine the association between their personality traits and *DAT1* polymorphisms.

Results

No statistically significant differences in allele or genotype frequencies of all investigated variants between HD patients and controls were observed (Table 1). In haplotype analysis, four haplotype blocks of *DAT1* were not associated with the development of HD (Fig. 1, Table 2). These *DAT1* polymorphisms did not influence novelty seeking and harm avoidance scores in HD patients (data are not shown).

Conclusion

This study suggests that the *DAT1* gene may not contribute to the risk of HD and specific personality traits in HD among Han Chinese.

Table 1. Gene location, minor allele frequencies and genotype frequencies of the investigated *DAT1* gene polymorphisms among patients with heroin dependence and controls

Variants	Gene location	Position reference dSNP	MAF (%)		p [b]	Allele [a]		Genotype, n (%)						p [c]
								HD (n=615)			Control (n=431)			
			HD	Control		1	2	2/2	1/1	1/2	1/1	1/2	2/2	
rs2550948	Promoter	1503444	15.4	13.0	0.128	***A***	G	10 (1.6)	169 (27.5)	436 (70.9)	9 (2.1)	94 (21.8)	328 (76.1)	0.107
rs6413429	Promoter	1500027	1.9	1.7	0.827	***T***	G	0 (0)	23 (3.7)	592 (96.3)	0 (0)	15 (3.5)	416 (96.5)	0.825
rs2652511	Promoter	1499389	15.9	14.0	0.253	***C***	T	12 (2.0)	171 (27.8)	432 (70.2)	9 (2.1)	103 (23.9)	319 (74.0)	0.368
rs2975226	Promoter	1498616	15.9	14.4	0.332	***A***	T	12 (2.0)	172 (28.0)	431 (70.1)	10 (2.3)	104 (24.1)	317(73.5)	0.367
rs6350	Exon 2	1496199	1.9	1.4	0.402	***A***	G	0 (0)	23 (3.7)	592 (96.3)	0 (0)	12 (2.8)	419 (97.2)	0.398
rs2981359	Intron 2	1495732	40.9	42.1	0.578	***G***	C	97 (15.8)	309 (50.2)	209 (34.0)	70 (16.2)	223 (51.7)	138 (32.0)	0.802
rs460000	Intron 3	1485825	48.5	45.8	0.235	***G***	T	150 (24.4)	296 (48.1)	169 (27.5)	85 (19.7)	225 (52.2)	121 (28.1)	0.189
rs460700	Intron 4	1482969	49.3	46.6	0.236	***T***	C	156 (25.4)	294 (47.8)	165 (26.8)	90 (20.9)	222 (51.5)	119 (27.6)	0.231
rs37020	Intron 6	1471374	36.2	34.3	0.386	***A***	C	79 (12.8)	287 (46.7)	249 (40.5)	48 (11.1)	200 (46.4)	183 (42.5)	0.653
rs27048	Intron 8	1465645	16.0	15.7	0.827	***T***	C	18 (2.9)	161 (26.2)	436 (70.9)	12 (2.8)	111 (25.8)	308 (71.5)	0.977
rs6347	Exon 9	1464412	12.1	11.6	0.721	***G***	A	13 (2.1)	123 (20.2)	479 (77.9)	2 (0.5)	96 (22.3)	333 (77.3)	0.059 [d]
rs11133767	Intron 13	1454580	8.5	10.1	0.201	***T***	C	5 (0.8)	94 (15.3)	516 (83.9)	9 (2.1)	69 (16.0)	353 (81.9)	0.193
rs27072	Exon 15	1447522	26.6	28.0	0.487	***T***	C	47 (7.6)	233 (37.9)	335 (54.5)	40 (9.3)	161 (37.4)	230 (53.4)	0.639

Variants	Gene location	Position reference dSNP	Allele [a]		Genotype, n (%)								p [c]
					HD (n=615)				Control (n=431)				
			1	2	Others	1/1	1/2	2/2	Others	1/1	1/2	2/2	
In8 VNTR [e]	Intron 8	1464855	***5R***	6R	7 (1.1)	19 (3.1)	166 (27.0)	423 (68.8)	3 (0.6)	9 (2.1)	129 (29.9)	290 (67.3)	0.541 [d]
3' VNTR [f]	Exon 15	1446863	***9R***	10R	22 (3.6)	5 (0.8)	75 (12.2)	513 (83.4)	26 (6.0)	2 (0.5)	55 (12.8)	348 (80.7)	0.250 [d]

MAF: Minor allele frequency; VNTR, 5R, 6R, 9R, 10R: 5-, 6-, 9-, 10-repeat allele.
[a] MAF in patients with HD compared with the control group using Pearson χ^2 test.
[b] Allele 1 that is italicized and bold indicates the minor allele, and only alleles with frequency higher than 1 % are showed.
[c] Genotype frequencies in patients with HD compared with the control group using Pearson χ^2 test.
[d] Statistical analysis was performed by Fisher's exact test.

Figure 1. The linkage disequilibrium (LD) structure between 12 polymorphisms in *DAT1* gene is presented. Numbers in boxes are the absolute D' values

Table 2. A logistic regression analysis of *DAT1* gene polymorphisms as risk factors for HD

Haplotype block 1		Frequency			Frequency		
3' VNTR	rs27072	Total HD	Total NC	p	Male HD	Male NC	p
10R	C	0.664	0.647	0.431	0.669	0.631	0.125
10R	T	0.264	0.279	0.459	0.255	0.296	0.075
9R	C	0.070	0.073	0.802	0.074	0.072	0.869

Haplotype block 2		Frequency			Frequency		
rs6347	In8 VNTR	Total HD	Total NC	p	Male HD	Male NC	p
A	6R	0.812	0.815	0.860	0.809	0.825	0.442
G	5R	0.100	0.101	0.988	0.105	0.096	0.552
A	5R	0.067	0.069	0.852	0.062	0.059	0.776
G	6R	0.021	0.015	0.374	0.023	0.021	0.731

Haplotype block 3			Frequency			Frequency		
rs37020	rs460700	rs460000	Total HD	Total NC	p	Male HD	Male NC	p
C	C	T	0.498	0.530	0.139	0.494	0.522	0.278
A	T	G	0.353	0.340	0.540	0.361	0.343	0.458
C	T	G	0.130	0.118	0.397	0.126	0.128	0.936

Haplotype block 4					Frequency			Frequency		
rs6350	rs2975226	rs2652511	rs6413429	rs2550948	Total HD	Total NC	p	Male HD	Male NC	p
G	T	T	G	G	0.839	0.855	0.340	0.842	0.850	0.686
G	A	C	G	A	0.135	0.115	0.118	0.133	0.126	0.665
A	A	C	T	A	0.016	0.012	0.367	0.016	0.010	0.340

附件二

P-25-002

2011 WFSBP in Prague

Dopamine Transporter Gene (*DAT1*) dose not influence the pathogenesis of Major Depressive Disorder and its personality trait.

Chang-Chih Huang [1]; San-Yuan Huang [1*]; Ru-Band Lu [2]; Mei-Chen Shih [1]; Che-Hung Yen

[1] Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[2] Institute of Behavior Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC

Introduction

Major depression (MD) is a complex psychiatric disorder involving multiple factors, including genetic and personality components. Although the dopamine transporter gene (*DAT1*) is a candidate gene for the etiology of MD, supporting data are limited. The aim of this study was to use 17 polymorphisms of *DAT1* to explore whether this gene is associated with MD and whether it influences personality traits in patients with MD.

Methods

DAT1 polymorphisms were analyzed in 1,017 unrelated Han Chinese subjects (582 MD patients and 435 controls). All participants were screened using the same assessment tool and all patients met the criteria of MD. A Tridimensional Personality Questionnaire was used to assess personality traits in 459 MD patients. In addition, patients with MD were divided into two clinical subgroups based on family history of affective disorders to reduce the clinical heterogeneity.

Results

We found a borderline association between controls and total MD (rs11133767 and rs27072) and between MD with family history vs. controls (rs403636, rs37020, and rs11133767); however, these differences were obscured after correction for multiple testing (Table 1). Haplotype analysis revealed that four haplotype blocks of *DAT1* were not associated with the development of MD (Figure). Furthermore, personality traits were not associated with *DAT1* polymorphisms (Table 2).

Conclusion

Despite the fact that several association tendencies were found between *DAT1* variants and MD or its clinical subgroups, we did not confirm a major role for the *DAT1* gene in the susceptibility to MD. In addition, *DAT1* does not seem to affect the personality traits observed in MD patients.

Table 1. Genotype distributions and allelic frequencies of the polymorphisms in the *SLC6A3 (DAT1)* gene between patients with major depression (MD) and controls in a Han Chinese population.

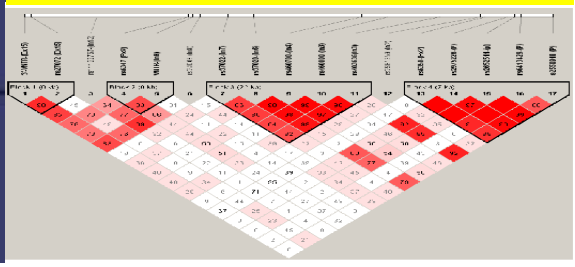
Variant	Position reference dSNP	Allele [a] 1	Allele [a] 2	MAF [a] (%) Control	MAF [a] (%) MD	p [b]	Genotype (%) Control (n=435) 1/1	1/2	2/2	Genotype (%) MD (n=582) 1/1	1/2	2/2	p [b]	Genotype (%) MD, F(+) (n=186) 1/1	1/2	2/2	p [b]
rs2550948	1503444(P)	A	G	13.1	15.4	0.167	10 (2.3)	94 (21.6)	331 (76.1)	16 (2.7)	147 (25.3)	419 (72.0)	0.339	9 (4.8)	43 (23.1)	134 (72.0)	0.205
rs6413429	1500027(P)	T	G	1.7	1.1	0.331	0 (0)	15 (3.4)	420 (96.6)	0 (0)	13 (2.2)	569 (97.8)	0.328	0 (0)	8 (4.3)	178 (95.7)	0.777
rs2652511	1499389(P)	C	T	14.1	16.2	0.235	10 (2.3)	103 (23.7)	322 (74.0)	15 (2.6)	158 (27.1)	409 (70.3)	0.420	8 (4.3)	50 (26.9)	128 (68.8)	0.243
rs2975226	1498616(P)	A	T	14.5	15.7	0.479	11 (2.5)	104 (23.9)	320 (73.6)	15 (2.6)	153 (26.3)	414 (71.1)	0.682	8 (4.3)	48 (25.8)	130 (69.9)	0.412
rs6350	1496199(E2)	A	G	1.4	1.1	0.743	0 (0)	12 (2.8)	423 (97.2)	0 (0)	13 (2.2)	569 (97.8)	0.741	0 (0)	8 (4.3)	178 (95.7)	0.454
rs2981359	1495732(In2)	G	C	42.2	43.2	0.675	71 (16.3)	225 (51.7)	139 (32.0)	112 (19.2)	279 (47.9)	191 (32.8)	0.376	31 (16.7)	89 (47.8)	66 (35.5)	0.641
rs403636	1491354(In3)	A	C	32.8	33.0	0.950	43 (9.9)	199 (45.7)	193 (44.4)	70 (12.0)	244(41.9)	268 (46.0)	0.364	27 (14.5)	63 (33.9)	96 (51.6)	0.016
rs460000	1485825(In3)	G	T	45.9	47.0	0.644	86 (19.8)	227 (52.2)	122 (28.0)	128 (22.0)	291 (50.0)	163 (28.0)	0.664	45 (24.2)	86 (46.2)	55 (29.6)	0.328
rs460700	1482969(In4)	T	C	46.7	48.2	0.523	91 (20.9)	224 (51.5)	120 (27.6)	139 (23.9)	283 (48.6)	160 (27.5)	0.502	47 (25.3)	81 (43.5)	58 (31.2)	0.185
rs37020	1471374(In6)	A	C	34.3	34.7	0.910	48 (11.0)	203 (46.7)	184 (42.3)	75 (12.9)	254 (43.6)	253 (43.5)	0.524	27 (14.5)	66 (35.5)	93 (50.0)	0.033
rs37022	1468629(In7)	T	A	49.9	48.7	0.632	115 (26.4)	204 (46.9)	116 (26.7)	136 (23.4)	295 (50.7)	151 (25.9)	0.421	53 (28.5)	87 (46.8)	46 (24.7)	0.822
rs27048	1465645(In8)	T	C	15.7	18.2	0.839	12 (2.8)	113 (26.0)	310 (71.3)	18 (3.1)	176 (30.2)	388 (66.7)	0.293	3 (1.6)	51 (27.4)	132 (71.0)	0.726[c]
rs6347	1464412(E9)	G	A	11.5	11.2	0.570	2 (0.5)	96 (22.1)	337 (77.5)	5 (0.9)	120 (20.5)	457 (78.5)	0.671[c]	1 (0.5)	42 (22.6)	143 (76.9)	0.963[c]
rs11133767	1454580(In13)	T	C	10.2	9.4	0.565	9 (2.1)	71 (16.3)	355 (81.6)	2 (0.3)	105 (18.0)	475 (81.6)	0.026[c]	0 (0.0)	42 (22.6)	144 (77.4)	0.025[c]
rs27072	1447522(E15)	T	C	27.7	25.3	0.235	40 (9.2)	161 (37.0)	234 (53.8)	30 (5.2)	234 (40.2)	318 (54.6)	0.037	9 (4.8)	76 (40.9)	101 (54.3)	0.162

Variant	Position reference dSNP	Allele[a] 1	Allele[a] 2	Genotype (%) Control (n=435) 1/1	1/2	2/2	other	Genotype (%) MD (n=582) 1/1	1/2	2/2	other	p [b]	Genotype (%) MD, F(+) (n=186) 1/1	1/2	2/2	other	p [b]
In8 VNTR [d]	1464855(In8)	5R	6R	10 (2.3)	129 (29.7)	293 (67.4)	3 (0.7)	13 (2.2)	185 (31.8)	375 (64.4)	9 (1.5)	0.542[e]	3 (1.6)	63 (33.9)	118 (63.4)	2 (1.1)	0.656[e]
3'-VNTR [d]	1446863(E15)	9R	10R	2 (0.5)	56 (12.9)	350 (80.5)	27(6.2)	2 (0.3)	72 (12.4)	470 (80.8)	38 (6.5)	0.986[e]	0 (0)	24 (12.9)	141 (75.8)	21 (11.3)	0.140[e]

Table 2. *DAT1* gene polymorphisms and specific personality traits in patients with MD. (459 MD patients completed TPQ)

Variants	Allele[a] 1	Allele[a] 2	MAF[a] (%)	TPQ score: Novelty seeking 1/1	Novelty seeking 1/2	Novelty seeking 2/2	Novelty seeking p[a]	Harm avoidance 1/1	Harm avoidance 1/2	Harm avoidance 2/2	Harm avoidance p[a]
rs2550948	A	G	14.9	16.08 (±3.85)	14.85 (±5.10)	14.03 (±5.57)	0.196	21.33 (±6.72)	20.53 (±5.84)	19.89 (±6.28)	0.497
rs6413429	T	G	1.3	0 (0)[b]	13.50 (±4.10)	14.31 (±4.46)	0.611	0 (0)[b]	22.67 (±6.21)	20.02 (±6.17)	0.143
rs2652511	C	T	15.9	16.08 (±3.85)	14.86 (±5.17)	14.01 (±5.56)	0.170	21.33 (±6.72)	20.70 (±5.87)	19.81 (±6.27)	0.314
rs2975226	A	T	15.5	16.08 (±3.85)	14.92 (±5.18)	13.99 (±5.55)	0.143	21.33 (±6.72)	20.76 (±5.92)	19.80 (±6.24)	0.272
rs6350	A	G	1.3	0 (0)[b]	13.50 (±4.10)	14.31 (±5.46)	0.611	0 (0)[b]	22.67 (±6.21)	20.02 (±6.17)	0.143
rs2981359	G	C	44.1	14.78 (±5.55)	14.12 (±5.61)	14.22 (±5.08)	0.606	19.85 (±6.29)	20.07 (±6.01)	20.27 (±6.39)	0.878
rs403636	A	C	33.7	13.02 (±5.01)	14.69 (±5.83)	14.28 (±5.13)	0.119	20.80 (±6.81)	19.30 (±6.65)	20.61 (±5.67)	0.068
rs460000	G	T	47.8	13.59 (±4.90)	14.77 (±5.74)	14.01 (±5.25)	0.148	20.21 (±6.44)	19.76 (±6.43)	20.58 (±5.47)	0.477
rs460700	T	C	49.0	13.73 (±4.85)	14.74 (±5.78)	13.98 (±5.25)	0.206	20.24 (±6.39)	19.75 (±6.40)	20.55 (±5.56)	0.493
rs37020	A	C	35.3	13.06 (±4.88)	14.54 (±5.90)	14.42 (±5.07)	0.153	20.95 (±6.23)	19.27 (±5.75)	20.63 (±5.46)	0.044
rs37022	T	A	49.1	14.54 (±4.97)	14.42 (±5.95)	13.79 (±4.73)	0.515	21.03 (±5.55)	19.64 (±5.14)	20.09 (±5.74)	0.155
rs27048	T	C	17.4	13.92 (±5.04)	14.43 (±5.34)	14.24 (±5.50)	0.917	19.15 (±5.89)	20.59 (±6.00)	19.91 (±6.27)	0.490
In8VNTR[c]	non6R	6R	—	13.50 (±6.79)	14.37 (±5.50)	14.28 (±5.36)	0.869	20.33 (±6.78)	20.10 (±6.03)	20.07 (±6.25)	0.990
rs6347	G	A	10.6	17.50 (±1.73)	14.29 (±6.14)	14.25 (±5.27)	0.494	15.25 (±2.87)	20.19 (±6.54)	20.11 (±6.11)	0.290
rs11133767	T	C	8.5	7.00[c]	14.41 (±5.77)	14.28 (±5.36)	0.400	6.00[b]	20.30 (±6.39)	20.08 (±6.11)	0.071
rs27072	T	C	24.9	13.75 (±4.38)	14.58 (±5.48)	14.13 (±5.50)	0.615	18.25 (±6.29)	20.91 (±6.12)	19.68 (±6.16)	0.040
3' VNTR[d]	non10R	10R	—	2.00[c]	14.73 (±5.59)	14.23 (±5.43)	0.058	16.00[b]	20.14 (±6.57)	20.09 (±6.11)	0.802

Figure : The linkage disequilibrium (LD) structure in *DAT1* gene.



附件三

2011 WFSBP in Prague

P-25-003

Serotonin transporter availability and the genetic polymorphism of SLC6A4 dose not associated with major depression and its severity

San-Yuan Huang[1], Kai-Jen Ho[2], Wen-Sheng Huang[3], Pei-Shen Ho[2], Mei-Chen Shih[1]

1. Department of Psychiatry, Tri - Service General Hospital , **National Defense Medical Center,** Taipei, Taiwan, R.O.C.,
2. Beitou Armed Forces Hospital, Taipei, Taiwan, ROC ,
3. Department of Nuclear medicine, Tri - Service General Hospital , National Defense Medical Center, Taiwan, R.O.C

Introduction

The serotonin transporter (SERT) is an important target to evaluate the pathophysiology of major depression (MD) and alcohol dependence (ALC). Brain imaging has been used to evaluate SERT expression in living individuals, with inconsistent results. The aim of this study was to use a more selective radioligand to explore whether SERT availability is associated with MD and whether genetic variants of the serotonin transporter gene (SLC6A4) influence SERT availability in patients with MD.

Objective

- **1. To measure the difference in brain SERT availability between MD patients and healthy controls using [123I]ADAM during depressive episode.**
- **2. To analysis the relationship between SERT availability and severity of depression.**
- **3. We hypothesised that brain SERT availability was affected by different polymorphisms of SLC6A4.**

Materials and methods

- **Subjects:**

A total of 64 individuals were enrolled in this study. Fifty-two subjects with MD and twelve age-matched healthy subjects were recruited.

- **SPECT procedure and analyses**

1. SPECT studies with [^{123}I]ADAM were performed within the first week of admission.
2. MRIs were co-registered to each SPECT image using the fusion modality of PMOD software. ROIs were marked in reference to the corresponding MRI. VOIs were counted after each ROI was drawn in each slice.

- **Genotyping of SLC6A4 :**

Two single nucleotide polymorphisms (SNPs) (rs6354 in exon 2 and rs25531 in the promoter region), and two variable number tandem repeats (VNTR) (STin2 in intron 2, 5-HTTLPR in the promoter region) were selected for genotyping.

Table 1. Demographic, clinical characteristics and triallelic genotype reclassification of depressive and healthy subjects

	Total MD		Healthy controls	
	Pure MD	MD/ALC		*p*-value
n	40	12	12	
Male: Female	13:27	7:5	8:4	0.071 [a]
Age	36.47±12.6	34.58±8.8	32.0±9.9	0.573 [b]
Marital status(% married)	42.5	33.3	41.7	0.934 [a]
Education(years)	12.6±3.6	11.1±3.8	15.7±1.2	0.002 [b]
Smoker : Non-smoker	19:21	12:0	5:7	0.001 [a]
Cigarettes per day	5.6±7.2	30.5±25.4	8.3±11.1	<0.001 [b]
HDRS	28.9±6.5	27.6±5.8		0.446 [c]
Triallelic genotype reclassification				
S'S': S' L' [d]	29:11	11:1	7:5	0.200 [a]
STin2				
12/12:non-12 repeated	30:10	11:1	9:3	0.574 [a]
rs6354 TT:GT	34:6	9:3	7:5	0.144 [a]

a Chi-square test with Fisher's exact test;; b Kruskal-Wallis test;; c Mann-Whitney test
d S' S' included LG/LG, LG/S, S/S; S' L' included LA/LG , LA/S

Results

- **In MD patients, the mean specific uptake ratio (SUR) values in four brain regions did not differ from those in controls (p>0.1). SERT availability was not affected by age, gender, severity of depression, duration of illness, smoking behaviours, and genetic variants of SLC6A4 among the three study groups (p>0.1).**

Table 2. Specific uptake ratio in brain regions of healthy controls, Pure MD and MD/ALC subgroups

Brain area	Healthy controls n = 12	Total MD n = 52	*p*-value[a]	Pure MD n = 40	MD /ALC n = 12	*p*-value[b]
Striatum	1.10±0.35	1.00 ± 0.42	0.427[c]	1.00±0.40	0.99±0.46	0.731[d]
Thalamus	1.32±0.54	1.05 ± 0.46	0.081[c]	1.00±0.42	1.25±0.57	0.061[d]
Midbrain	1.86±0.46	1.64 ± 0.66	0.281[c]	1.63±0.65	1.67±0.73	0.549[d]
Pons	1.39±0.34	1.25 ± 0.44	0.305[c]	1.20±0.42	1.40±0.49	0.209[d]

All entries for brain specific uptake ratio in this table presented as mean ± SD; a *p* value of independent test; b*p* value of one-way ANOVA test;; c Controls vs. Total MD; ; dControls vs. Pure MD vs. MD/ ALC

Figure 1. Depression Severity and SERT availability

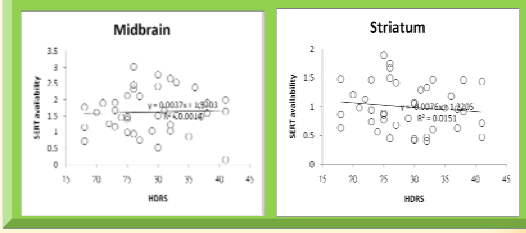


Figure 2. SUR of 123I-ADAM in examined brain regions of S'S' homozygotes (grey boxes) versus L'S' heterozygotes (white boxes) of the 5- HTTLPR in healthy controls, pure MD and MD/ALC.

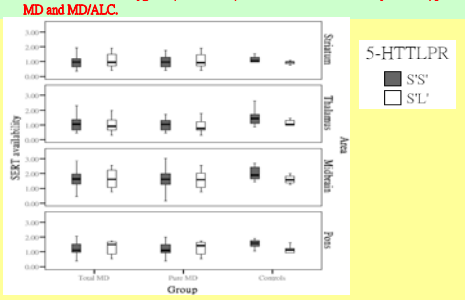


Figure 2. SUR of ^{123}I-ADAM in examined brain regions of S'S' homozygotes versus S'L' heterozygotes of the 5-HTTLPR in total MDD, pure MDD and healthy subjects. Horizontal lines indicate group medians. Boxes indicate interquartile range. Figure 2. SUR of ^{123}I-ADAM in examined brain regions of S'S' homozygotes versus S'L' heterozygotes of the 5-HTTLPR in total MDD, pure MDD and healthy subjects. Horizontal lines indicate group medians. Boxes indicate interquartile range.

Conclusions

- **SERT availability could be a biomarker in the development of MD; however, we did not prove this hypothesis in the present [123I]ADAM brain imaging study. Further studies using different populations, different radio-ligands, and more homogenous subgroups in different course of MD should be performed.**