알쯔하이머병의 약물유전학적 지표

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Potential implications of pharmacogenetics

- **Efficacy**

- **Safety**

- **Selection of drugs**

Cholinesterase Inhibitors

- **Efficacy**

  - **Only 50%** (Schneider & Farlow, 1997)

  - **10-20%** (Cacabelos, 2006)

- **Safety**

  - **Side-effects, intolerance, non-compliance > 60%**

Who will show a greater response to ChEIs?

- **Severity** : mild AD patients

- **Sex** : Male

- **Symptoms** : those who showed less impairment on visual-spatial and lexical-semantic functioning

- **Physiological markers** : EEG, CBF…

- **Genetic markers**
  - Genes associated with drug metabolism
  - Genes associated with AD

CYP2D6 genotypes in AD

- CYP2D6 locus : 100 different alleles

  - Extensive metabolizers (51.6%)

  - Intermediate metabolizers (32.3%)

  - Poor metabolizers (9.0%)

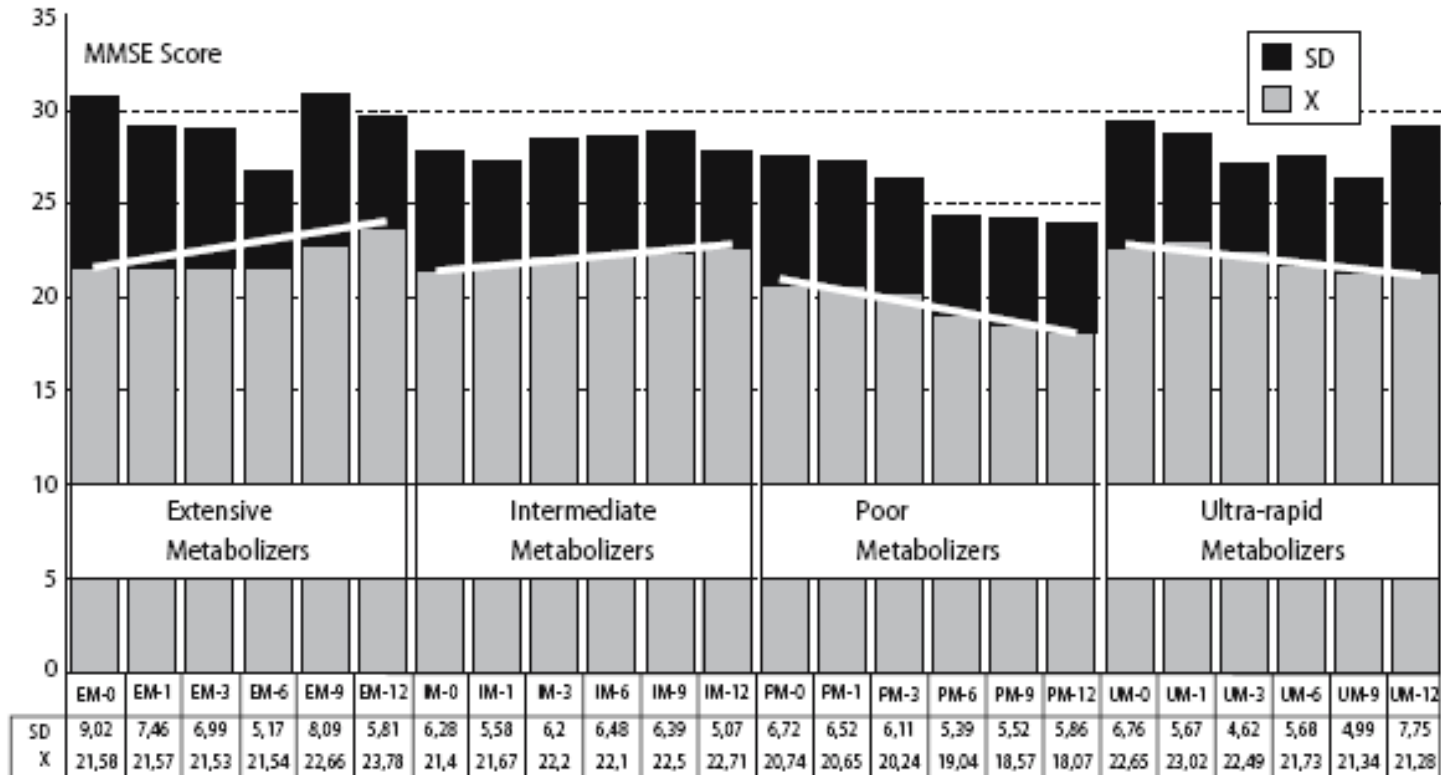 - Ultra-rapid metabolizers (7.1%)

Effect of a *CYP2D6* polymorphism on the efficacy of donepezil in patients with Alzheimer disease

Neurology® 2009;73:761-767

- G alleles of rs1080985

  - nonresponders vs responders : 58.7% vs 34.8%

CYP2D6 genotypes in AD

(Cacabelos, 2007)

EM : *1/*10 genotype > *1/*1 genotype

Genes associated with AD pathogenesis

- **Amyloid beta metabolism**

  APP, PS1, PS2, APOE, ACT, A2M, LRP, VLDLR, BCHE

- **Inflammation or apoptosis**

  IL-1, IL-6, TNF-**α**, HLA-A-A2

- **Oxidative stress**

  CYP2D6, NOS2, NOS3, transferrin

APOE and response to ChEIs

- Poirier et al. (1995)

  ε 4 carrier : less response to tacrine

- Richard et al.(1997)

  ε 4 carrier : more response to donepezil

- Less response in ε 4 carrier

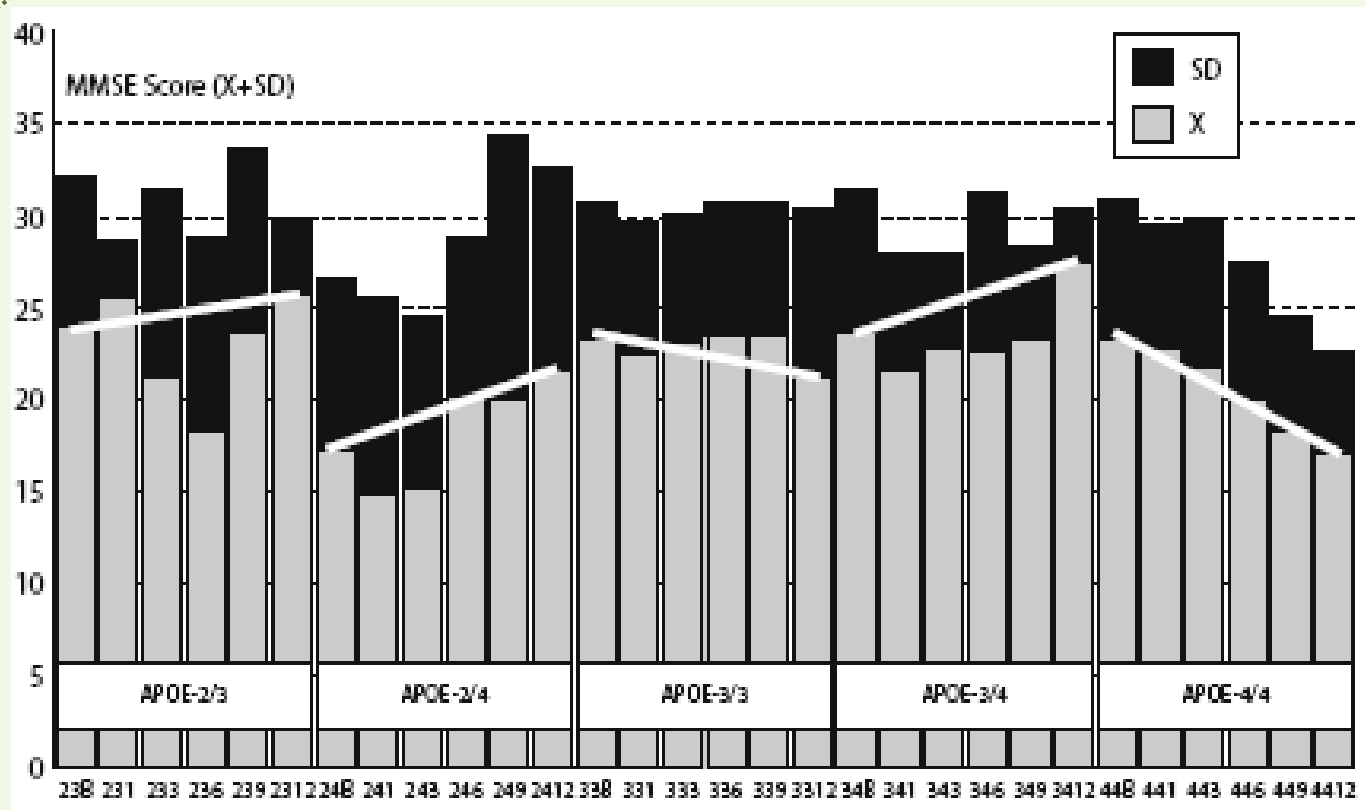 Farlow et al.(1998), Sjogren et al.(2001)

- More response in ε 4 carrier

  Bizzarro et al.(2005), Farlow et al.(2004), Choi et al.(2008)

- No difference

  MacGown (1998), Rigaud (2000), Aerssens (2001), Suh (2006)

APOE and response to Tx

(Cacabelos, 2007)

Clinical trial to Korean population

A Prospective, Double-Blind, Community-Controlled Comparison of Three Doses of Galantamine in the Treatment of Mild to Moderate Alzheimer's Disease in a Korean Population

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Effect of *ApoE* Genotype on Response to Donepezil in Patients with Alzheimer's Disease

Seong Hye Choi[a]   Sang Yun Kim[c]   Hae Ri Na[b]   Byung-Kun Kim[d]
Dong Won Yang[e]   Jay C. Kwon[f]   Mee Young Park[g]

Subjects & methods in our study

- 13 University hospitals and 2 hospitals for the elderly
- Probable AD patients (CDR 0.5-2)
- 199 were registered and 135 finished the trial
- 26 weeks
- CERAD, NPI, GDS
- APOE ε4 carriers : 39.4%

Demographic and clinical characteristics

Patients	Age	Sex (M/F)	Education	CDR score
Total (n=199)	74.6(±6.5)	63/136	5.2(±4.9)	0.81±0.40
12 weeks (n=148)	74.6(±6.5)	46/102	5.0(±4.6)	0.80±0.39
26 weeks (n=135)	74.2(±6.5)	44/91	5.1(±4.7)	0.81±0.40

Our results

MMSE		baseline	12wks	26wks	P time	P interx
	Apoε2/ε3or ε3/ε3	17.91±4.42	18.40±4.68	18.48±4.78	0.1336	
	Apoε2/ε4or ε3/ε4	16.34±4.74	17.17±5.56	17.65±5.84	0.7671	
	Apoε4/ε4	15.07±5.15	14.70±3.77	13.50±4.83	0.3541	
	P genotype	0.0279	0.0099	0.0016		0.5516

Word		baseline	12wks	26wks	P time	P interx
List	Apoε2/ε3or ε3/ε3	1.71±1.99	2.15±1.97	2.14±2.15	0.0575	
Recall	Apoε2/ε4or ε3/ε4	1.23±1.36	1.39±1.70	1.82±1.70	0.4815	
	Apoε4/ε4	0.78±0.97	1.10±1.10	1.30±1.63	0.358	
	P genotype	0.7312	0.2168	0.4556		0.348

Our results

Word		baseline	12wks	26wks	P time	P interx
List	Apoε2/ε3or ε3/ε3	4.96±3.06	5.32±3.12	5.21±3.28	0.0051	
Recognition	Apoε2/ε4or ε3/ε4	3.79±2.82	4.26±2.99	3.90±3.01	0.1291	
	Apoε4/ε4	2.28±2.09	2.20±2.69	2.80±2.65	0.6872	
	P $_{genotype}$	0.0897	0.0098	0.1763		0.6011
	Apoε2/ε4or ε3/ε4+Apoε4/ε4	3.51±2.75	3.89±3.02	3.68±2.95	0.0945	
	P $_{genotype}$	0.0415	0.0027	0.0938		0.2685

APOE and response in anxiety and depression

(Cacabelos, 2007)

- Response : ε2/ε4 > ε2/ε3 > ε3/ε3 > ε3/ε4 > ε4/ε4
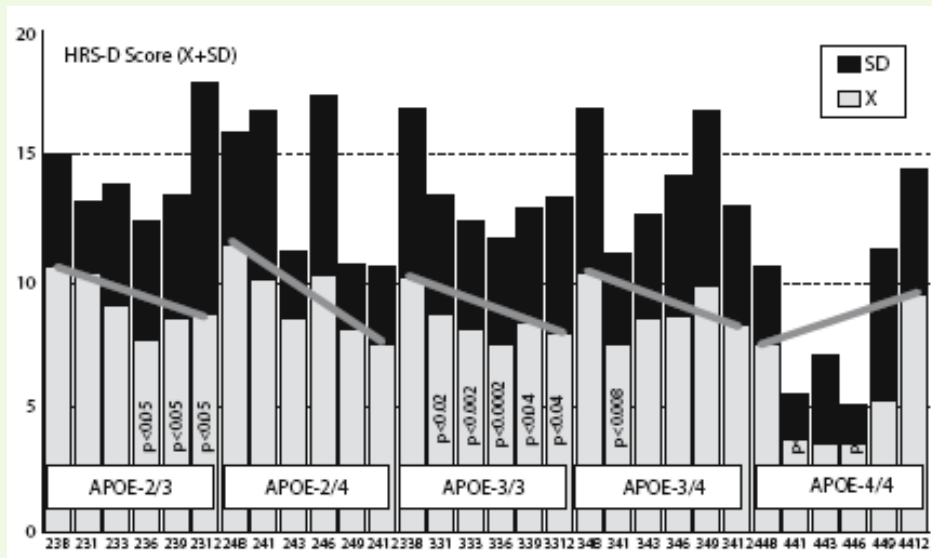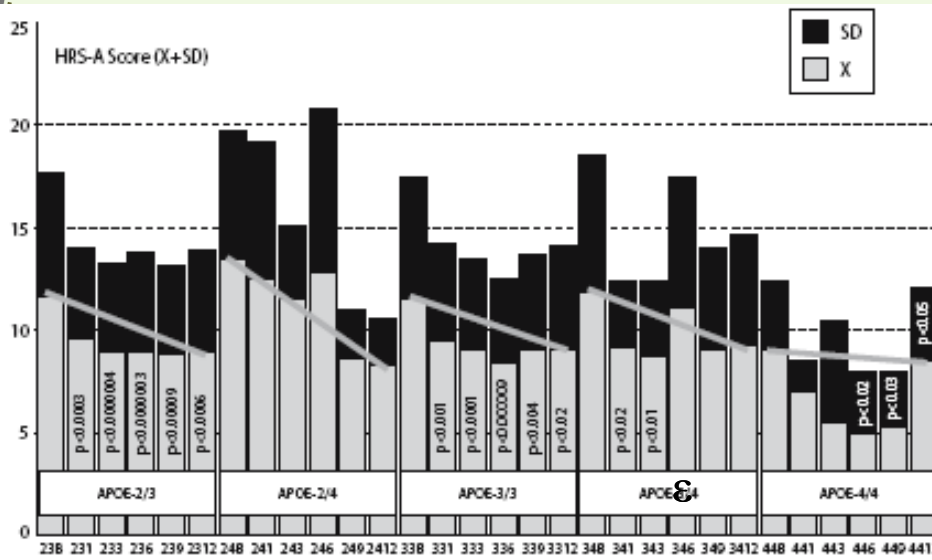
Our results

NPI1		baseline	12wks	26wks	P time	P interx
Apoε2/ε3or ε3/ε3		0.83±2.42	0.55±2.02	0.23±0.92	0.2404	
Apoε2/ε4or ε3/ε4		1.30±3.26	0.77±2.55	0.75±2.42	0.0137	
Apoε4/ε4		1.00±1.79	1.40±2.63	1.60±3.86	0.7082	
P genotype		0.4957	0.6819	0.1864		0.1097
Apoε2/ε4or ε3/ε4+Apoε4/ε4		1.25±3.04	0.89±2.55	0.92±2.74	0.0417	
P genotype		0.2656	0.6987	0.08		0.0989

GDS		baseline	12wks	26wks	P time	P interx
Apoε2/ε3or ε3/ε3		12.99±6.95	11.25±6.04	11.29±6.62	0.0187	
Apoε2/ε4or ε3/ε4		13.62±6.28	12.44±6.97	12.75±6.26	0.7205	
Apoε4/ε4		12.64±5.04	13.00±3.19	11.18±5.23	0.4585	
P genotype		0.7915	0.2699	0.2584		0.4795
Apoε2/ε4or ε3/ε4+Apoε4/ε4		13.43±6.05	12.54±6.43	12.39±6.04	0.8318	
P genotype		0.6535	0.1139	0.1998		0.4449

AchE, BChE and ChAT gene & response

- Scacchi et al. (2009)
  - No difference in BChE and ChAT
  - A/A genotype of AChE : more response
- Belsa et al. (2006)
  - Wild type BChE carrier : more response to rivastigmine than donepezil
  - K-variant Carrier : no differences
- Harold et al. (2006)
  - Promoter region of ChAT is associated with ChEI response

ChAT gene studies in Korean population

Choline acetyltransferase G +4 A polymorphism confers a risk for Alzheimer's disease in concert with Apolipoprotein E ε4

Ki-Woong Kim[a], Young-Ju Suh[b], Woong-Yang Park[c], Jin-Hyeong Jhoo[d], Dong-Young Lee[e], Jong-Chul Youn[f], Kwang-Hyuck Lee[c], Jeong-Sun Seo[c], Jong-Inn Woo[e,g,*]

ApoE-ε 4-dependent association of the choline acetyltransferase gene polymorphisms (2384G>A and 1882G>A) with Alzheimer's disease

Sangmee Ahn Jo[a,b,*], Kyungsook Ahn[a], Ji-Hyun Kim[a], Byung-Hak Kang[a], Eunkyung Kim[a], Inho Jo[a], Doh Kwan Kim[c]

Our results

MMSE		baseline	12wks	26wks	P time	P interx
	ChAT GG	17.24±4.75	17.61±5.00	17.51±5.54	0.5234	
	ChAT GA+AA	17.11±4.46	18.10±5.00	18.68±4.46	0.0287	
	P genotype	0.8587	0.4513	0.1632		0.0951

Word		baseline	12wks	26wks	P time	P interx
List	ChAT GG	1.48±1.86	1.89±1.89	1.90±1.89	0.1322	
Recall	ChAT GA+AA	1.51±1.55	1.74±1.88	2.17±2.22	0.6371	
	P genotype	0.6235	0.641	0.8378		0.9394

Interactions of genes

- APOE & CYPD26

APOE $\varepsilon4/\varepsilon4$ convert CYPD26 extensive metabolizers into poor metabolizers after 1 year treatment

- APOE, PS1 & PS2

(Cacabelos, 2003)