Pharmacogenetic application in the treatment of depression

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Antidepressants: mechanisms

5-HT, Norepinephrine, (dopamine)

Changes in 5-HT, NE, DA receptor stimulation, neuronal activity

Changed neuronal sensitivity, growth factors (BDNF), gene expression, cell number & morphology

Antidepressant effects take time: 2–6 weeks

We need markers for predicting treatment response of individuals, which can be incorporated into pharmacogenetic treatment algorithms
Possible genetic markers for antidepressant response; monoamine-related genes (examples)

- **HTR1A** (serotonin receptor 1A)
  - In Asian: Fluvoxamine (Suzuki et al. 2004, Kato et al. 2009), Fluoxetine (Hong et al. 2006)

- **HTR2A** (serotonin receptor 2A)
  - In Caucasian: Citalopram (Uher et al. 2009), Duloxetine (Perlis et al. 2009)
  - In Asian: Paroxetine (Kato et al. 2006)

- **COMT** (catechol-O-methyltransferase)
  - In Caucasian: Mirtazapine (Szegedi et al. 2005), Citalopram (Arias et al. 2006), Duloxetine (Perlis et al. 2009), Paroxetine (Benedetti et al. 2009)
  - In Asian: Milnacipran (Yoshida et al. 2008)

- **SLC6A2** (norepinephrine transporter)
  - In Caucasian: Nortriptyline (Uher et al. 2009)
  - In Asian: Milnacipran (Yoshida et al. 2004), Nortriptyline (Kim et al. 2006)
Pharmacogenetic studies about monoamine-related genes

**EFFECT OF SEROTONIN RECEPTOR 2A GENE POLYMORPHISM ON MIRTAZAPINE RESPONSE IN MAJOR DEPRESSION**

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**SLC6A4**

SSRIs
MAOIs
SNRIs

**ll genotype was associated with long-term effect of antidepressant**

Lee, et al. (Psychiatr Genet, 2004)

**HTR2A**

Citalopram

G allele is associated with MDD and citalopram response

Choi, et al. (Neuropsychobiol, 2005)

**HTR2A**

Mirtazapine

The 5-HTR2A -1438A/G polymorphism are associated with sleep symptoms improvement after 2 weeks of medication with mirtazapine (marginal)


**ADRA2A**

Mirtazapine

No association with the therapeutic response to mirtazapine

Lee, et al., (Brain research, 2009)

Pharmacogenetic studies about monoamine-related genes

**Table 1.** Genotype, allele, and allele carrier frequencies of the -1438A/G polymorphism of 5-HT2A among patients with MDD and normal controls

<table>
<thead>
<tr>
<th></th>
<th>Genotype</th>
<th>Allele</th>
<th>Allele carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>AG</td>
<td>GG</td>
</tr>
<tr>
<td>MDD (n = 71)</td>
<td>11 (15.5)</td>
<td>37 (52.1)</td>
<td>23 (32.4)</td>
</tr>
<tr>
<td>Controls (n = 157)</td>
<td>40 (25.5)</td>
<td>88 (56.1)</td>
<td>29 (18.5)</td>
</tr>
</tbody>
</table>

Genotypes: $\chi^2 = 6.473$, df = 2, $p = 0.039$; alleles: $\chi^2 = 5.589$, df = 1, $p = 0.018$ (OR = 0.618, 95% CI = 0.414-0.922); allele carriers: $\chi^2 = 5.383$, df = 1, $p = 0.020$ (OR = 0.473, 95% CI = 0.248-0.879). Figures in parentheses indicate percentages.

Luciferase reporter assay of -1438A and -1438G in the SH-SY5Y cells (epithelial cells derived from neuroblastoma)

-1438

G

LUC

A

LUC

Relative luciferase activity

0

1

3

5

7

9

11

p = 0.022

Weeks

Sleep scores

p = 0.041

A+ - A-

0

1

2

3

4

5

6

7

8

p = 0.041

Time effect: F=32.030, p=0.0001; Genotype effect: F=4.371, P=0.037;

Time – Genotype effect: F=0.780, p=0.538

The $\chi^2$-test was used to detect significant differences.

<table>
<thead>
<tr>
<th></th>
<th>A+</th>
<th>A-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Non-responders</td>
<td>52</td>
<td>6</td>
</tr>
</tbody>
</table>

Remitters

<table>
<thead>
<tr>
<th></th>
<th>A+</th>
<th>A-</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Non-remitters

<table>
<thead>
<tr>
<th></th>
<th>A+</th>
<th>A-</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>26</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

$\chi^2 = 2.978$, p = 0.026

$\chi^2 = 4.512$, p = 0.034

OR = 0.324, 95% CI = 0.112-0.936

Patient subgroups were defined after considering clinical response and remission at the 4th week. Responders were defined as having a decrease in the HAMD total score of at least 50% after 4 weeks of medication. Remitters were defined as subjects having an HAMD total score of 7 or less points after 4 weeks of medication. Figures in parentheses indicate percentages.
Barriers for clinical application

1) The most of the pharmacogenetic studies were retrospective

2) Genetic context are quite different between ethnics

3) Many different classes of AD are used to treat MDD

It might be necessary that

• comparative analyses for pharmacogenetic profiles between ethnic groups or between the classes of antidepressants

• prospective studies for pharmacogenetic treatment guideline including known genetic and environmental factors, as well as discovery and validation of novel candidates.
Aim

- To evaluate the genetic association of genetic polymorphisms with treatment response to the different classes of AD (citalopram and mirtazapine) in 194 Korean patient with MDD
- To establish 1st draft of pharmacogenetic antidepressant treatment algorithm
• SSRI
  • increases 5-HT in the synaptic cleft
  • inhibit the 5-HT transporter
  • produces side effects less frequently than TCA
  • the most frequently prescribed antidepressant in Korea

• NaSSA
  • increases 5-HT and noradrenaline
  • block noradrenaline a2-autoreceptors, noradrenaline a2-heteroreceptors, 5-HTR2 and 5-HTR3
  • faster onset of efficacy than citalopram
  • side effects: increased appetite and weight gain
Candidate genes

• Receptors
  – HTR1A (G272D, -1019G>C)
  – HTR2A (-1757G>A, -1438A>G)
  – HTR2C (2103T>G, 3896T>C, -759C>T)
  – ADRA2A (-1291C>G)

• Serotonin transporter
  – SLC6A4 (LPR, VNTR)

• Neurotrophic factor
  – BDNF (V66M, +132C>T)

• Pharmacokinetic
  – CYP2D6 (P34S)
  – CYP2C19 (-636G>A, -681G>A)

• Signal transduction
  – GNB3 (+825T>C, IVS2-123C>A, IVS2-156G>A)

• Others (final effector of HPA system)
  – GCCR (-6297A>G, +1830C>G)
Association between SNPs and treatment response

-\log (P value)

P = 0.01
P = 0.05

1w
2w
4w
8w

Association between SNPs and treatment response

-\log (P value)

P = 0.01
P = 0.05

5HTT VNTR
BDNF V66M
GCCR-1830
Association between SNPs and % reduction of HAMD21

-log (P value)

1w

2w

4w

8w

SNPs:
- 5HTT VNTR
- BDNF V66M
- GCCR-1830
Summary I

- **GCCR+1830C>G** was associated with the response to either citalopram or mirtazapine at 4w

- **BDNF V66M** was associated with the response to citalopam at 8w

- **5HTT VNTR** was associated with the response to mirtazapine at 4 and 8w
The association of GCCR+1830C>G with treatment response to citalopram or mirtazapine

**Citalopram**

The association of NR3C1 SNP with responses to citalopram at 4w

<table>
<thead>
<tr>
<th>Response to citalopram</th>
<th>NR3C1 SNP genotypes</th>
<th>Total</th>
<th>P</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Response</td>
<td>CC</td>
<td>26 (86.7%)</td>
<td>4 (13.3%)</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Response</td>
<td>CC+GG</td>
<td>19 (57.6%)</td>
<td>14 (42.4%)</td>
<td>33 (100%)</td>
</tr>
</tbody>
</table>

Comparison of HAM-D score changes by citalopram treatment according to NR3C1 SNP genotypes

- **P = 0.048**

**Mirtazapine**

The association of NR3C1 SNP with responses to mirtazapine at 4w

<table>
<thead>
<tr>
<th>Response to mirtazapine</th>
<th>NR3C1 SNP genotype</th>
<th>Total</th>
<th>P</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Response</td>
<td>CC</td>
<td>46 (56.1%)</td>
<td>36 (43.9%)</td>
<td>82 (100%)</td>
</tr>
<tr>
<td>Response</td>
<td>CC+GG</td>
<td>75 (67.0%)</td>
<td>37 (33.0%)</td>
<td>112 (100%)</td>
</tr>
</tbody>
</table>

Comparison of HAM-D score changes by mirtazapine treatment according to NR3C1 SNP genotype

- **P = 0.025**

MDD patients possessing G allele showed **better response** to citalopram treatment

MDD patients possessing CC genotype showed **better response** to mirtazapine treatment
The comparison of response status by citalopram or mirtazapine according to genotypes of GCCR+1830C>G

<table>
<thead>
<tr>
<th>GCCR+1830C&gt;G</th>
<th>Treated drug</th>
<th>Response status</th>
<th>Total</th>
<th>P</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NRs</td>
<td>Rs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>Citalopram</td>
<td>57.8% (26)</td>
<td>42.2% (19)</td>
<td>100% (45)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>38.0% (46)</td>
<td>62.0% (75)</td>
<td>100% (121)</td>
<td></td>
</tr>
<tr>
<td>CG+GG</td>
<td>Citalopram</td>
<td>22.2% (4)</td>
<td>77.8% (14)</td>
<td>100% (18)</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>49.3% (36)</td>
<td>50.7% (37)</td>
<td>100% (73)</td>
<td></td>
</tr>
</tbody>
</table>

- **Citalopram** may be **more suitable** than mirtazapine for treating of MDD patients possessing **G allele (CG+GG)**
- **Mirtazapine** may be **more suitable** than citalopram for treating of MDD patients possessing **CC genotype**

→ The GCCR genotype can be a good genetic marker to decide treatment strategies
The 1st draft of pharmacogenetic algorithm for antidepressant treatment

GCCR+1830C>G

- CC
  - Mirtazapine

- CG or GG
  - Citalopram
However, V66M was associated with the treatment response to citalopram; The patients having M allele showed better response than who having V allele did.
V66M was not associated with the clinical outcomes by mirtazapine treatment
The 1st draft of pharmacogenetic algorithm for antidepressant treatment

GCCR+1830C>G

CC
- Mirtazapine
  - Responder
    - continue
  - Non-responder
    - BDNF V66M
      - VV
      - VM or MM
        - switching to citalopram
  - other methods (switching to other drugs, ECT, combination, augmentation, optimization)

CG or GG
- Citalopram
5HTT VNTR was associated with the treatment response to mirtazapine; The patients who were 12-repeat homozygotes showed better response
Association between 5HTT VNTR and response to citalopram treatment

5HTT VNTR was not associated with the clinical outcomes by citalopram treatment
The 1\textsuperscript{st} draft of pharmacogenic algorithm for antidepressant treatment

- **GCCR+1830C>G**
  - **CC**
    - **Mirtazapine**
      - **Responder**
      - **Non-responder**
      - **BDNF V66M**
        - **VV**
          - switching to citalopram
        - **VM or MM**
          - other methods (switching to other drugs, ECT, combination, augmentation, optimization)
  - **CG or GG**
    - **Citalopram**
      - **Responder**
      - **Non-responder**
      - **5-HTT VNTR**
        - **12.12.**
          - switching to mirtazapine
        - **12.10. +10.10.**
          - other methods (switching to other drugs, ECT, combination, augmentation, optimization)
Summary II

- MDD patients possessing *G* allele on GCCR+1830C>G → better response to citalopram
- the subjects having CC genotype on GCCR+1830C>G → better response to mirtazapine.
- M allele carriers on BDNF V66M → better response to citalopram treatment (not to mirtazapine).
- 12-repeat homozygotes on 5HTT VNTR → better response to mirtazapine treatment (not to citalopram).

Using the results, we could suggest a draft of pharmacogenetic algorithm for citalopram or mirtazapine treatment
Limitations

• Small sample size (especially citalopram-treated group);
could not exclude the possibility of false positive
→ need replication of the results and evaluation of the biological functions of the polymorphisms

• Retrospective study design;
it was an explorative study
→ need to be confirmed using prospective clinical study

• Restricted to citalopram and mirtazapine;
too low informative to use in clinical practice
→ need inclusion of escitalopram (SSRI), venlafaxin (SNRI), duloxetine (SNRI), etc.

• The small number of candidate genes;
could not reflect entire pathophysiology of MDD and the action mechanism of antidepressant
→ need evaluation of other candidate genes and environmental factors
Conclusions

• Many different classes of AD are used to treat MDD → a reason for that pharmacogenetics is hard to be used in clinical practice

• The comparative study for different AD → the 1st marker (GCCR)
  Differently associated polymorphisms with each drugs → the 2nd markers (5HTT and BDNF) in pharmacogenetic treatment algorithm

Although there are several limitations of the study,

this is the first suggestion for the application of pharmacogenetics in treatment of MDD
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