# 강박장애의 유전이상과 치료적 적용

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## Genetic studies of OCD

- Family risk studies
- Twin studies & Adoption studies
- Segregation analysis
- Genetic linkage analysis
- Association studies

## Twin Studies

- Inouye et al.*(1965)*
  - Concordance rate MZ(80%) > DZ(50%)
- Carey & Gottesman*(1981)*
  - Concordance rate MZ(87%) > DZ(47%)
- Rasmussen & Tsung*(1983)*
  - MZ twin(65%)

✓ Environmental + genetic factor – important in OCD

## Family Studies I

Family study method

- Lewis et al.*(1935)*
  - 37.2% of 1st degree relatives – obsessive traits
- Kringlen et al.*(1965)*
  - 50% of parent of OCD patient – nervous
- Rasmussen et al.*(1986)*
  - 4.5% of parents – OCD
  - 11.5% of parents – obsessive traits

## Family Studies II

Family history method

- Bellodi et al.*(1992)*
  - 3.4% of 1st degree relatives – OCD
- Nicolini et al.*(1993)*
  - 4.9% of 1st degree relatives – OCD for DSM-III-R
- Paul et al.*(1995)*
  - First degree relatives of OCD(10.3%) > of normal(2%)

## Segregation Analyses

- Mode of transmission(Mendelian pattern)
- Nicoli et al.*(1991)*
  - Not AD or AR
- Cavallini et al.*(1998)*
  - Not AD or AR

✓ Mixed model – multigenetic background

## Linkage Analyses

- Weissbeck et al.*(1989)*
  - 3 generation family
  - OCD+tic
  - LOD score 1.3 in 4p13 chromosomal region
- Brett et al.*(1995)*
  - Genes for DA, 5-HT receptor and enzyme gene
  - Negative results

## Association Studies I

- Serotinin transporter
  - Inconsistent findings
  - Positive results
    - o European-American OCD Vl ↑ than control(TDT studies)*(Begel et al. 1999, McDougle et al. 1998)*
  - Negative results
    - o Mexican*(Nicolini et al. 1996, Camarena et al. 2001)*
    - o Caucasian*(Altemus et al. 1996)*
  - No study of Oriental population
- 5-HT1Dß
  - G861C & T371G
  - Preferential transmission of the G allele in affecteds(TDT study) *(Mundo et al. 2000)*
  - Negative study in G861C(TDT study)*(Di Bella et al. 2002)*

## Association Studies II

- MAO-A
  - EcoRV polymorphism in exon 14
    - o '1' allele – more frequent in OCD female(HRR study) *(Camarena et al. 2001)*
  - Exon 8 polymorphism
    - o 297CGG allele – more frequent in OCD male(HRR study) *(karayiorgou et al. 1999)*

## Association Studies III

- COMT
  - G158A in 22q11
  - Val-Met substitution(high-low activity)
  - Karayiorou et al.*(1997)*
    - o COMT-L/L – odd ratio 5.91 esp. in male
  - Schindler et al.*(2000)*
    - o Homozygosity(TDT study) – higher trend in OCD
  - Alsobrook II et al.*(2002)*
    - o COMT-L(TDT, HRR study) – higher in female not male

## Association Studies IV

- Dopamine transporter
  - 40 bp VNTR(3~11 repeats, 7 allele)
  - Frisch et al.*(2000)* & Hemmings et al.*(2003)*
    - o No association between DAT1 & OCD
- Dopamine 4 receptor
  - Cruz et al.*(1997)*
    - o DRD4 7 repeat allele – ass. with OCD
  - Milet et al.*(2003)*
    - o DRD4 2 repeat – protective factor of OCD?
  - Frisch et al.*(2000)*
    - o No association between DRD4 & OCD

## Genetics of OCD in Korean

| | OCD patients | Controls | p-value |
|---|---|---|---|
| **Genotype** | N=95 | N=119 | |
| s/s | 59(62.1%) | 69(58.0%) | |
| l/s | 33(34.7%) | 46(38.7%) | 0.83 |
| l/l | 3( 3.2%) | 4( 3.4%) | |
| S-type(s/s) | 59(62.1%) | 69(58.0%) | 0.58 |
| L-type(l/s+l/l) | 36(37.9%) | 50(420.5%) | |
| **Allele** | N=190 | N=238 | |
| s | 151(79.5%) | 184(77.3%) | 1.00 |
| l | 39(20.5%) | 54(22.7%) | |

*Kim SJ & Kim CH*

Sex distribution and genotype and allele frequency of 5-HTT gene polymorphism in early- & late-onset OCD patients

| | Early-onset group (age<18) | Late-onset group (age≥18) | p-value |
|---|---|---|---|
| **Genotype** | N=45 | N=40 | |
| s/s | 23(51.1%) | 30(75.0%) | 0.07 |
| l/s | 20(44.4%) | 9(22.5%) | |
| l/l | 2( 4.4%) | 1 (2.5%) | |
| S-type(s/s) | 23(51.1%) | 30(75.0%) | 0.03 |
| L-type(l/s+l/l) | 22(48.9%) | 10(25.0%) | |
| **Allele** | N=90 | N=80 | **p-value** |
| s | 66(73.3%) | 69(86.3%) | 0.06 |
| l | 24(26.7%) | 11(13.8%) | |

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Four factors solution for OCD patients

| | Factor 1 (Hoarding /repeating) | Factor 2 (Contaminat-ion/cleaning) | Factor 3 (Aggressive /sexual) | Factor 4 (Religious /somatic) |
|---|---|---|---|---|
| **Obsessions** | | | | |
| aggressive | | | 0.719 | |
| contamination | | 0.705 | | |
| sexual | | | 0.840 | |
| hoarding | 0.549 | | | |
| religious | | | | 0.767 |
| symmetry | | | | |
| somatic | | | | 0.830 |
| **Compulsions** | | | | |
| cleaning | | 0.808 | | |
| checking | | | | |
| repeating | 0.764 | | | |
| counting | 0.832 | | | |
| ordering | 0.540 | | | |
| hoarding | 0.623 | | | |
| % of explained variance | 34.00 | 11.12 | 9.96 | 7.70 |

Comparisons of factor scores between OCD patient with S- and L-genotype

| Factor score | S-group(s/s) (N=59) | L-group(l/s+l/l) (N=36) | p-value |
|---|---|---|---|
| **Factor 1** | -0.018±0.904 | -0.003±0.1.163 | 0.98 |
| **Factor 2** | 0.063±1.071 | -0.109±0.869 | 0.44 |
| **Factor 3** | 0.082±0.994 | -0.142±1.010 | 0.31 |
| **Factor 4** | -0.273±0.860 | 0.472±1.060 | 0.001 |

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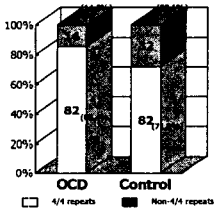
## Genotype frequency of DRD4 gene polymorphism in OCD & controls I

| Genotype | OCD patients (N=96) | Controls (N=114) | p-value |
|---|---|---|---|
| 2/2 | 1( 1.0%) | 0( 0.0%) | |
| 2/4 | 10(28.6%) | 25(21.9%) | |
| 2/5 | 1( 1.0%) | 1( 0.9%) | |
| 4/4 | 82(85.4%) | 82(71.9%) | 0.09 |
| 4/5 | 0( 0.0%) | 3( 2.6%) | |
| 4/6 | 1( 1.0%) | 1( 0.9%) | |
| 4/7 | 1( 1.0%) | 2( 1.8%) | |

*Kim SJ & Kim CH*

## Genotype frequency of DRD4 gene polymorphism in OCD & controls II

| Genotype | OCD (N=96) | Control (N=114) | P- value |
|---|---|---|---|
| Non-4/4 | 14 (14.6%) | 32 (28.1%) | 0.02 |
| 4/4 | 82 (85.4%) | 82 (71.9%) | |

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## Comparisons of factor scores between OCD patients with 4/4 repeats & Non-4/4 repeat genotype of DRD4

| Factor score | Non-4/4 repeats (N=13) | 4/4 repeats (N=73) | p-value |
|---|---|---|---|
| Factor 1 | 0.452±0.988 | -0.773±1.003 | 0.07 |
| Factor 2 | -0.368±1.186 | 0.035±0.922 | 0.21 |
| Factor 3 | -0.275±0.650 | 0.049±1.030 | 0.37 |
| Factor 4 | -0.040±1.122 | 0.028±0.951 | 0.60 |

Mann-Whitney U test

## Genotype frequency of DAT1 gene polymorphism in OCD & controls I

| Genotype | OCD patients (N=99) | Controls (N=110) | p-value |
|---|---|---|---|
| 9/10 | 5( 5.1%) | 10( 9.1%) | |
| 10/10 | 92(92.9%) | 95(86.4%) | 0.30 |
| 10/11 | 2( 2.0%) | 5( 4.5%) | |
| **Allele** | (N=198) | (N=220) | |
| 9 | 5( 2.5%) | 10( 4.5%) | |
| 10 | 191(96.5%) | 205(93.2%) | 1.0 |
| 11 | 2( 1.0%) | 5( 2.3%) | |

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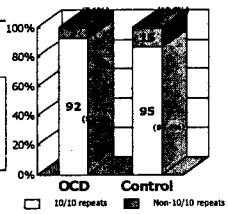
## Genotype frequency of DRD4 gene polymorphism in OCD & controls II

| Genotype | OCD (N=99) | Control (N=110) | P- value |
|---|---|---|---|
| Non-10/10 | 7 ( 7.1%) | 15 (13.6%) | 0.18 |
| 10/10 | 92 (92.9%) | 95 (86.4%) | |

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## Comparisons of factor scores between OCD patients with 4/4 repeats & Non-4/4 repeat genotype of DRD4

| Factor score | Non-10/10 repeats (N=6) | 10/10 repeats (N=78) | p-value |
|---|---|---|---|
| **Factor 1** | 0.535±1.354 | -0.045±0.993 | 0.36 |
| **Factor 2** | 0.238±0.925 | -0.050±0.987 | 0.43 |
| **Factor 3** | 0.260±1.089 | -0.026±0.979 | 0.53 |
| **Factor 4** | -0.127±1.033 | 0.033±0.984 | 0.84 |

Mann-Whitney U test

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## Gene & Treatment Response

- Very rare
- 2 reports
  - serotonin transporter polymorphism
    - Billett et al.*(1997)* – German
    - Bella et al.*(2002)* – Italian

**Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene**

EA Billett[1], MA Richter[2], N King[1], A Heils[3], KP Lesch[3] and JL Kennedy[1]

[1]Neurogenetics Section, Anxiety Disorders Clinic, Clarke Institute of Psychiatry, University of Toronto, Toronto, Canada M5T 1R8; [2]Department of Psychiatry, University of Wurzburg, 97080 Wurzburg, Germany

Table 1 Allele and genotype frequencies for the serotonin transporter polymorphism in OCD patients and controls

| | n | Freq. of allele 1 | Genotype | | | | P value (2 d.f.) |
|---|---|---|---|---|---|---|---|
| | | | 1-1 | (1/1) | 1-2 | (1/s) | 2-2 (s/s) | |
| OCD patients | 72 | 0.64 | 0.32 | 0.44 | 0.24 | | |
| Controls | 72 | 0.56 | 0.25 | 0.61 | 0.14 | | 0.115 |
| SRI responders | 57 | 0.64 | 0.32 | 0.44 | 0.25 | | |
| SRI non-responders | 21 | 0.60 | 0.38 | 0.43 | 0.19 | | 0.818 |
| Clomipramine responders | 24 | 0.54 | 0.29 | 0.50 | 0.21 | | |
| Clomipramine non-responders | 10 | 0.75 | 0.50 | 0.50 | 0 | | 0.229 |
| Fluoxetine responders | 23 | 0.52 | 0.30 | 0.43 | 0.26 | | |
| Fluoxetine non-responders | 14 | 0.54 | 0.29 | 0.50 | 0.21 | | 0.919 |

*Molecular psychiatry(1997)*

## Obsessive-Compulsive Disorder, 5-HTTLPR polymorphism and treatment response

D Di Bella S Erzegovesi MC Cavallini L Bellodi

Table 2 Demographic features of Obsessive-Compulsive patients divided according to 5-HTTLPR genotypes

| | 5HTTPR genotypes | | |
|---|---|---|---|
| | l/l | l/s | s/s |
| Number of patients | 24 (27.9%) | 45 (44.9%) | 23 (23.9%) |
| Sex: male/female | 12/12 | 19/26 | 13/8 |
| Mean age ± SD (yrs) | 32.45 ± 12.43 | 31.44 ± 9.3 | 34.83 ± 13.39 |
| Mean age at onset ± SD (yrs) | 19.12 ± 10.44 | 17.35 ± 6.03 | 16.78 ± 7.01 |
| TD coding/none | 1 (4.2%) | 5 (11.9%) | 2 (9.52%) |
| Positive Family history for OCD | 5 (20.8%) | 15 (35.7%) | 4 (19.05%) |
| Positive Family history for TD | 0 | 3 (11.4%) | 0 |
| YBOCS scores before treatment ($T_0$) | 30.1 ± 5.5 | 29.7 ± 6.6 | 26.9 ± 7.45 |
| YBOCS scores after treatment ($T_1$) | 20.0 ± 8.22 | 16.3 ± 7.64 | 17.3 ± 8.93 |
| YBOCS obsession scores $T_0$ | 15.1 ± 2.40 | 15 ± 3.67 | 14.5 ± 3.64 |
| YBOCS obsession scores $T_{1a}$ | 9.4 ± 4.3 | 9.1 ± 4.9 | 9.1 ± 4.41 |
| YBOCS compulsion scores $T_0$ | 14.3 ± 3.37 | 14.6 ± 3.54 | 12.8 ± 5.27 |
| YBOCS compulsion scores $T_{1a}$ | 9.3 ± 4.22 | 7.1 ± 4.94 | 4.7 ± 4.47 |
| Non responders rate (< 35%) | 58% | 43.9% | 42.9% |

l = wild-type allele; s = allele carrying the 44-bp insertion

*The Pharmacogenomics Journal(2002)*

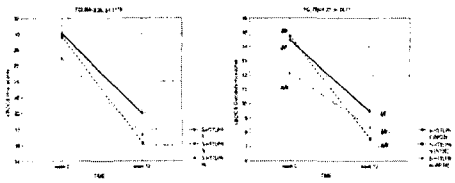

Figure 1 Patterns of change in YBOCS scores during treatment with fluvoxamine in 5-HTTLPR genotype groups. See text for further details.



Figure 2 Patterns of change in YBOCS compulsions scores during treatment with fluvoxamine in 5-HTTLPR genotype groups in patients with OCD and without a TIC co-diagnosis. See text for further details.

YBOCS compulsions score reduction

l/s>s/s and l/s>l/l

*The Pharmacogenomics Journal(2002)*