공황장애에서 유전학

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Genetics of fear

- Cause of abnormal sensitive fear network
  : Inherited tendency for fearfulness ?
- Fear associated chromosomes
  - Mouse chromosome 1,12,15 (Flint등 1995)
  - Other studies : chromosome 1

Genetic evidence of PD

- Genetic evidence ?
  - In first-degree relatives, prevelance of PD ↑
  - Twin study (monozygotic vs. dizygotic)
    : high concordance rate for monozygotic twins
- Susceptibility to panic,
  not PD itself is inherited
  : Unusually sensitive fear network is inherited

Types of Genetic studies

- Genetic epidemiology
  - Family study, Twin study, Adoption study
    (Segregation analysis : Mode of transmission 결정)
- Molecular genetic research
  - Linkage study : parametric, nonparametric
  - Quantitative trait loci
  - Association study

Family studies of PD

Study	Date	Probands	Morbidity risks in 1st degree relatives
Crowe 등	1983	41 PD 41 controls	PD 17.3% PD 1.8%
Harris 등	1983	20 AgPh 20 PD 20 controls	PD 7.7% PD 20.5% PD 4.2%
Noyes 등	1986	40 AgPh 40 PD 20 controls	PD 8.3%, AgPh 11.6% PD 17.3%, AgPh 1.9% PD 4.2%, AgPh 4.2%

AgPh = agoraphobia

Mode of Transmissioin I

- Highly penetrant autosomal dominant single major locus (Pauls 등 1980)
- Single locus model과 Multifactorial polygenic transmission model 모두 가능(Crowe 등 1983)
- Dominant & recessive model 둘 다 적합하나, 비유전적 전달방식모형은 기각됨 (Vieland 등, 1996)

Mode of Transmissioin II

- Cavallini 등 (1999) : "Additive model"
  - 165 가족을 분석한 결과, 불완전한 투과도를 보임
    유전 전달과 발현에 다른 부가적인 요인이 관여
  - CO_2 normosensitive vs. CO_2 hypersensitive
    : CO_2 hypersensitive PD 환자의 family는
    dominant model을 따름.
- 결국 수직적 유전전달은 분명하나, 그 방식은 불확실하다

Twin studies

Study	Date	Interview type	Twin Pairs,N	Concordance Rate MZ	DZ
Torgersen	1983	DSM-	85 PD	31%	0%
Skre 등	1993	DSM-	49 PD	42%	17%
Perna 등	1997	DSM	60 PD	73%	0%
			SPA	57%	43%

- MZ twins의 일치율이 DZ twins에 비해 최소 2.5배지만, 항상 1 보다 작고, 대개 40% 이하.

→ 환경적 요인도 중요 요인임!

Linkage studies

- Useful for finding genes in AD, AR, or X-linked disorders
- Crowe et al(1987)
  Tested for 29 genetic markers in 26 families
  Alpha-haptoglobin locus(16q22): not replicated
- Fyer and Weissmann (1999)
  - Linkage with a marker on chromosome 20p
  - Parent-of-origin effect : 모계 유전빈도 > 2배

Linkage studies
-candidate genes-

- GABA
  - Reduced benzodiazepine binding sites in PD
  - No evidence of linkage between PD and 8 of 13 subunits in the $GABA_A$ receptor gene (Crowe 등 1997)
- 5 Adrenergic receptor loci (Wang 등 1992)
- POMC(pro-opiomelanocortin)
  : Corticotropin synthesis에 관여(Crowe 등, 1987)
- 5-HTT promoter region (Hamilton 등 1999)

Association studies

- 환자군과 대조군에서 표지 유전자 빈도 비교

장점: 1) multifactorial
2) detecting genes of small effects
단점: 1) 위양성의 가능성이 높음
2) population stratification

대안: 부모를 포함시키는 연합연구
→ TDT(Transmission Disequilibrium Test)
HRR(Haplotype Relative Risk)

Association studies in PD I

- Serotonergic system
  - VNTR polymorphism의 경우 long allele이 combined anxiety disorder와 연관(Ohara 1999)
  - 5-HTTLPR의 경우 short allele이 harm avoidance에 관계한다고 하며(Lesch 1996), 그렇지 않다는 보고도 있다.(Nakamura 1997)
  - 5_HTTLPR의 short allele, MAO-A long allele에 CCK-4 induced panic attack을 줄인다.(Maron 2004)

Association studies in PD II

- CCK(Cholecystokinin) system
  - Controversy Mutation in CCK_A & CCK_B receptor gene
  - Promoter region of CCK 연관(Wang, 1998) → not replicated(Hosing, 2004)
  - N-acetyl-*B*-glucosaminidase (a marker for serotonergic activity) : higher in PD with a CCK mutation than in patients without the mutation
    → suggests 2 PD subtypes?
    (CCK 이상 vs. Serotonin 이상)

Association studies in PD III

- Noradrenergic system
  - Increased functionally active MAO-A gene promoter alleles in female patients with PD (Deckert, 1999)
  - Positive linkage between A_{2a} adenosine receptor gene and PD (Hamilton 2004)
    : Caffeine = Adenosine receptor antagonist
    → adenosine-mediated inhibition of NE release를 차단 (panic-inducing drug)

Association studies in PD IV

- Positive association between COMT and poor Tx. Response(Woo, 2002)
- Positive association between COMT and PD in female(Domschke, 2004)
- Controversy serotonin receptor and PD
- Duplication of chr. 15p24-q26(DUO25)
- cAMP responsive element modulator(CREM)

Results from other genetic studies

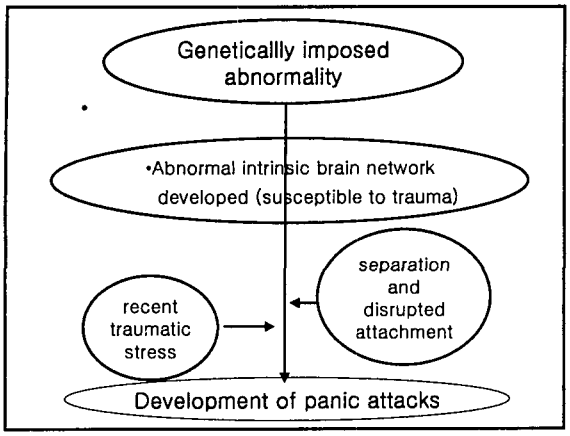
- Chromosome 20q13.2-q13.3
  - Association between low voltage EEG and anxiety disorders
  - CHRNA4 (Nicotinic acetylcholine receptor alpha 4 subunit) is located in the same location
    → No difference in the allele frequency

Conclusion of association studies

Multifactorial mode of inheritance를 지지하며, 공황장애의 유전적 기초를 밝히는 데 시사점을 제시하고 있음.

Environmental basis of PD

- Early disruption of attachment
  : associated with later development of PD
- 10세 이전에 어머니가 사망 : 7배
  부모와 헤어졌거나 10세 이전에 부모 이혼: 4배
- More child sexual and physical abuse in PD patients



Other candiadate genes for PD

- Panic-specific gene?
- Anxiety-specific gene?
  - NE transporter gene
  - CRF-related gene
  - Catecholamine-related gene
    - : MAO, COMT