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Searching for Vulnerability Genes of Schizophrenia

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The genetic factor has been proved to be the major etiological factor of schizophrenia. The heritability was estimated to be 0.70. Up to now, the mode of transmission of schizophrenia is still uncertain. The most plausible genetic model is of oligogenetic model. There may be 3 to 5 genes responsible for the genetic vulnerability of schizophrenia. The locations of vulnerable genes of schizophrenia are currently under active search in the field of psychiatric molecular genetic study.

Research team of the Department of Psychiatry, National Taiwan University Hospital has kept on carrying the study on searching for the vulnerability genes of schizophrenia using the Taiwan Chinese samples. The samples of families with co-affected sib-pairs with schizophrenia were recruited systematically. DNA samples were collected, the transformed lymphoblastoid cell-lines were set up. The clinical data of the recruited families members were collected. DNA bank, cell-line bank and clinical data bank were established in he Department of Psychiatiy, National Taiwan University Hospital.

Laboratory work of molecular genetic study of this research team included positional cloning and candidate gene approaches. There are some suggestive linkage evidences in our study over the chromosome regions of 6p21-24, 8p21-22, 15q13-14, and 22q12-13, though not to statistical criteria for significant linkage. The research on 1q 31-41 markers could not rule out the possibility of linkage.

In order to sharpen the method of molecular genetic approach in searching for vulnerability genes of schizophrenia, increasing sample size and further refining of phenotype is crucial for promising results.

A 5-year nation-wide collaborative work, sponsored by the NIMH, U.S.A., to collect families with co-affected sib-pairs with schizophrenia has been going on for 2 years. The research is a collaborative work between the Department of Psychiatry, National Taiwan University Hospital and Harvard Medical School. Total of 600 families is scheduled to collect. DNA samples, cell-lines and clinical data of DIGS, FIGS, as well as neuropsychological testing data were collected.

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To increase homogeneity of clinical phenotype of schizophrenia, we have carried a subtype study by using symptom clustering and patient clustering techniques based on follow-up assessment of clinical psychopathology using reliable rating scale of PANSS. Besides, the study on definition of endophenotype is also carried out by using neurobiological correlates, e.g. attention test, Wisconsin Card Sorting Test (WCST), working memory, as well as evoked potential indicator.

Candidate gene approach included polymorphism of DRD2, DRD4 receptor genes, cytosolic phospholipase A2 gene, and SCA1 gene, in this laboratory showed negative results. Further studies in this area will include polymorphism of N-methyl-D-aspartate (NMDA) and nicotinic receptor gene.

With the increase of sample size and more phenotypic indicators, high throughput genotyping work and genetic analysis by more powerful genetic statistical method are needed.

Key words: genes of schizophrenia