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Taiwan Schizophrenia Linkage Study: The Field Study

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One possible reason of the inconsistent results of linkage analyses of schizophrenia, a complex disorder, was mainly due to the small sample size of studies. This Taiwan Schizophrenia Linkage Study (TSLS) was designed to collect a large family sample with at least two affected siblings of a single ethnicity. The 17.6 millions of Taiwanese Chinese, age over 15, was the sample population, and 78 psychiatric hospitals or health centers participated in this TSLS program. Before data collection started, every study subject signed the informed consent. The ascertainment protocol for data collection included blood sample, structured Diagnostic Interview for Genetic Studies (DIGS), Structured Interview for Schizotypy (SIS), scales for assessment of positive and negative symptoms (SAPS, SANS), and continuous performance test (CPT), Wisconsin card sort test (WCST) of neuropsychological functions. We have contacted 831 families for this study and 607 families, comprised 2,490 subjects, were successfully recruited. The recruitment rate was 38.4% from the estimated total of 1,582 families with at least two affected siblings. These collected family samples were fairly evenly distributed all over Taiwan. Those 2,490 study subjects (1,283 male, 1,117 female) comprised 1,568 siblings (mean age 35.7 years old) and 922 parents (mean age 63.6 years old). Of these 1,568 siblings, 1,258 (80.2%) were affected (male 795, female 463), and the mean age of onset was 22.6 years old. Among 922 parents, 65 were affected (male 14, female 51) and the age of onset was 33.1 years old. This TSLS demonstrated a successful establishment of an efficient research infrastructure to collect a large nation-wise sample of schizophrenic family for genetic linkage study.

KEY WORDS: schizophrenia; linkage analysis; affected sibling pairs; field study; continuous performance test; Wisconsin card sort test

INTRODUCTION

Family, twin, and adoption studies have unequivocally demonstrated that genetic vulnerability is a major contributing factor in the etiology of schizophrenia [Gottesman et al., 1982; Cloninger, 1989; Kaufman and Malaspina, 1991; Tsuang and Faraone, 1994, 1997; Owen et al., 2003]. Segregation analysis has not been able to determine the mode of inheritance, and linkage analyses of schizophrenia have produced equivocal results [Riley and McGuffin, 2000; Badner and Gershon, 2002], with some studies suggesting linkage to specific loci but others that do not.

Among the many reasons for these inconsistent results, there are two major factors: (1) schizophrenia is most likely caused by many genes interacting with environmental factors [Gottesman and Shields, 1967; Faraone and Tsuang, 1985; Cloninger, 1989, 1994; McGue and Gottesman, 1989; Risch, 1990a; Suarez et al., 1994]. The effect of each disease gene would be small. The sample sizes of most studies have been small [Suarez et al., 1994; Lander and Kruglyak, 1995] with not enough statistical power for linkage analysis; (2) most samples have been complex in ethnic composition, which would compromise the power of linkage analyses if there was disease locus heterogeneity between strata or if analyses could not be adjusted for ethnic differences in marker allele frequencies

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[Collaborative Study on the Genetics of Asthma (CSGA), 1997; Cloninger, 1998]. In this situation, non-replication of linkage results among different studies is expected [Suarez et al., 1994; Altmüller et al., 2001].

Based on these observations, changes to the designs of genetic linkage studies of complex disorders such as schizophrenia have been proposed [Cloninger, 1994]. It was suggested that the linkage strategy for locating multiple genes, each of small to moderate effect, should recruit a large enough sample of pairs of affected siblings and their families recruited from a multisite study, rather than looking for major genes in large extended pedigrees [Risch, 1990b]. With this research orientation, the NIMH Genetics Initiative [Cloninger, 1997] was established [Cloninger et al., 1998].

We proposed the Taiwan Schizophrenia Linkage Study (TSLS), in response to the NIMH request for application (RFA) entitled "Molecular Genetics of Mental Disorders," to help clarify the genetics of schizophrenia. Our goal was to collect a large sample of a single ethnicity (Taiwanese Han Chinese), providing adequate statistical power for identifying genomic regions, which may harbor loci conferring susceptibility to schizophrenia. TSLS was designed to collect and clinically characterize a large family sample of 600 Taiwanese Chinese families with at least two siblings meeting DSM-IV criteria for schizophrenia. Up to now, there were 478 affected sib-pairs data in the NIMH Genetic Initiative of Schizophrenia (http://zork.mustl.edu/nimh/sz.html). This TSLS will contribute the other estimated 600 sib-pairs and this will, then, provide a large enough data bank of sib-pair family of schizophrenia for genetic study.

METHODOLOGY

Taiwan is about 160 km from the southern coast of the Chinese mainland in the Pacific Ocean. Taiwan Island is 394 km long and 144 km wide at its broadest point (Fig. 1). The total population of Taiwan as of the year 2002 was 22,484,364. The total number of households is 6,760,785 for Taiwanese Han Chinese. On an average, there are 3.3 persons per household; of those, 2.6 are 15 years old. There was a population of 17,555,280 ages over or equal to 15 years old, as the sampling population of this TSLS, excluding aborigine population of 319,063. The cases of aborigines were excluded from this study by family history of aborigine origin. Either father or mother with history of aborigine lineage was as the exclusion criteria.

Fig. 1. Distribution of study hospitals and proband recruitment rate based on population over 15 years of age.

The lifetime prevalence of schizophrenia in the population over 15 years old is 0.3% [Lin, 1953; Hwu et al., 1989]. The prevalence of schizophrenia in first degree relatives was assumed to be 2.5% (Weinberg's shorter method) to 3.9% (Kaplan–Meir estimate) [Hwu, 1999a; Chang et al., 2002], and the age range of probands identified would be 15–64 years. Using the family risk of 3.4%, the number of families with affected sib pairs was expected to be 1,582. It was expected that, due to refusals, inadequate diagnostic information, mortality, and other factors, approximately 40% of these, or about 600 families, could be recruited for the project.

Infrastructure of the TSLS Program

The basic infrastructure of the TSLS study group consisted of six evenly distributed data collection field research centers (FRCs), which were established throughout Taiwan: (1) Taipei FRC (the TSLS research headquarters) at the Department of Psychiatry, National Taiwan University Hospital and Medical College, National Taiwan University; (2) Northern Taiwan FRC at the National Taoyuan Psychiatric Center; (3) Middle Taiwan FRC at the National Tsaotun Psychiatric Center; (4) Southern Taiwan FRC at the Department of Psychiatry, National Cheng-Kung University; (5) Kaoping FRC at the Kai-Suan Psychiatric Hospital, Kaohsiung City; and (6) Eastern FRC at the Yu-Li Veterans Hospital and National Yu-Li Hospital. The FRCs are located at nuclear hospitals of the national psychiatric service catchment areas under the agreement of these hospitals' administrative system. These nuclear hospitals are the teaching and service centers of all psychiatric service institutions distributed in the specific catchment areas. The number of study sample recruitment and the quality of data collections were thus assured. Blood samples could be delivered conveniently to the cell repository center at Rutgers University, New Jersey from Taiwan.

Three levels of research meetings were organized: (1) meetings at the FRC level provided the platform for presenting TSLS specific aims. Agreement of the research program was achieved at this meeting level; (2) meetings at the catchment area level established case recruitment procedures and established communication protocol between the research headquarter, the FRCs, and the local participating hospitals; and (3) meetings at the participating hospital or health station level informed the meaning and goals of TSLS and the practical process of proband recruitment to all the members of clinical service team.

Ascertainment of Samples

The ascertainment procedure began by identifying suitable probands with clinical record of schizophrenia or depressive type of schizoaffective disorder from the clinical service settings or the medical records of the participating hospitals or the community psychiatric service stations. The potential proband had to have at least one other sibling affected with the similar diagnosis according to the family history. The depressive type of schizoaffective disorder was included as the ascertainment diagnosis because it was considered as one manifestation of the schizophrenia susceptibility genes based on the data of family study [Baron et al., 1982; Kendler et al., 1986; Maier and Lichtermann, 1991; Maj et al., 1991; Bertelsen and Gottesman, 1995]. If the proband and any other affected siblings were twins, the zygosity was checked and monozygotic twins were excluded. It was necessary to have both parents

available in this study. If only one parent was available, then another non-affected sibling would be necessary for recruitment. If both parents met criteria for schizophrenia or the depressive type of schizoaffective disorder, the family was excluded. All non-affected siblings were encouraged to participate in this study for data collection. During the initial history taking, the parental lineage of aborigine was evaluated. If any one of the parents or grandparents of the potential proband had the suspected lineage of aborigine, this case was excluded.

After the clinical staff identified the candidate proband, oral consent from the potential proband and family for participating in the study was obtained. The clinical service staff would, then, fill out the initial screening sheet to record clinical diagnoses of the proband and the other affected siblings, the twin history of the family, the addresses and telephone numbers for contacting the other family members, and the hospitals providing psychiatric services for other affected siblings or the affected parents, if any.

The assigned research psychiatrist at the participating hospital would make a clinical screening diagnosis on the proband case following a semistructured psychiatrist diagnostic assessment (PDA) procedure [Hwu, 1999b], using a specialist diagnostic assessment sheet (SDAS) based on the criteria of the 4th edition of the Diagnostic and Statistical Manual (DSM-IV) [American Psychiatric Association, 1994]. These interview data were supplemented with clinical information if needed, by reviewing the initial screening sheet and medical records for making a clinical diagnosis for initial screening of the proband. After the research psychiatrist completed and signed the final screening sheet, it was promptly sent to the research headquarters by fax to check for potential double registration, as the recruitment procedure covered all hospitals simultaneously. When research headquarters approved the potential proband and family, they were registered as a potential family for ascertainment, and the final screening sheet was passed to the field research manager to assign field research interviewers. Field research interviewers visited the candidate proband and the family members including the parents, the other affected and non-affected siblings. Before data collection started, every study subject signed the informed consent document, which has been thoroughly explained by the field research interviewers.

The TSLS program was approved by the Department of Health and Human Services office for protection from research risks, with the assurance to comply with 45CFR 46 (assurance number S-16276-01). It was also approved by the National Taiwan University Hospital's Internal Review Board (assurance number 87001) of Human Studies, where the TSLS research headquarter is located.

Ascertainment Instruments for Data Collection

All probands, the other affected and non-affected siblings, and the parents who agreed to participate in the TSLS program completed a series of research procedures. The standard research protocol included the following components: (1) a blood sample; (2) a structured Diagnostic Interview for Genetic Studies (DIGS) and family history assessment for axis I disorder; (3) assessment of positive and negative symptoms; and (4) assessment of schizotypal personality disorder. Subjects with a lifetime diagnosis of any schizophrenic disorders were not assessed for schizotypal personality disorder, as the purpose of this assessment was for measuring the non-psychotic phenotypes related to schizophrenia. The neuropsychological functions of sustained attention and executive function were assessed by personnel supported by a grant from the National Health Research Institute and National Science Council, Taiwan.

The structured Mandarin Chinese version of the DIGS [Chen et al., 1998b] was for collecting a detailed assessment of the course of illness, and for careful assessment of substance abuse and mood symptoms [Nurnberger et al., 1994; Faraone et al., 1996]. The DIGS data were crucial for making the final best estimate diagnoses of schizophrenia and related disorders by excluding the possibility of substance-related psychoses, bipolar type of schizoaffective disorder, and psychotic mood disorders. The DIGS also assessed dimensions of psychopathology using the Scales for Positive and Negative Symptoms (SANS and SAPS) [Andreasen, 1984a,b]. The symptom assessment was done at the time of interview. The axis II Cluster A Personality pictures, including schizotypal, schizoid, and paranoid personality disorder, were assessed using the modified version of the Structured Interview for Schizotypy (SIS) [Kendler et al., 1989]. The Family History for Genetic Study (FIGS) and the clinical summary of all available medical records were also used when making the best estimate of the final diagnoses. The FIGS interviews were obtained from every family members who participated in this TSLS study.

The neuropsychological functions of sustained attention, as assessed by the continuous performance test (CPT) [Rosvold et al., 1956], and executive functions as assessed using the Wisconsin card sort test (WCST) [Robinson et al., 1980; Heaton, 1981; Lin et al., 2000] were obtained from the study subjects. The impaired executive functions are considered to be of value in genetic study of schizophrenia [Goldberg et al., 1987; Weinberger et al., 1988; Koren et al., 1998; Egan et al., 2001; Wolf et al., 2002]. Besides, impaired sustained attention, as assessed by the CPT, was found to be a possible endophenotype indicator of schizophrenia [Nuechterlein et al., 1986; Harvey et al., 1996; Chen et al., 1998b, 2004; Cornblatt et al., 1999; Liu et al., 2002]. The effect of age, education, and sex on the performance of CPT was adjusted based on a community sample of 345 subjects [Chen et al., 1998a], while that on the WCST was adjusted on 211 health-screening controls [Chiu CH, unpublished data]. The z scores adjusted for these demographic features of these performance indicators would be used for study analyses. The CPT and WCST data could be used to separate subtypes of schizophrenia with and without impaired CPT or WCST for association and/or linkage analyses. Besides, the data of CPT and WCST could also be used in quantitative transmission disequilibrium test for significant association of specific risk haplotype with schizophrenia.

Blood samples were drawn and sent, within 24 hr, to the cell repository at Rutgers University, New Jersey, for lymphoblastoid cell transformation and cell line reservation. A subset of blood samples was sent for DNA extraction to the research headquarters in the Department of Psychiatry of National Taiwan University.

After candidate field interviewers were selected, all candidates had to complete a 3-week training program. The program provided interviewers with (1) a working knowledge of the current medical model of psychiatry, the DSM-IV diagnostic system, and the structure of all interview schedules; (2) expertise in the administration and scoring of the DIGS, FIGS, SIS, SAPS, SANS, and neuropsychological function assessments of CPT and WCST using computer programs. The inter-rater reliability of SAPS and SANS among the interviews was examined after the training course. Fourteen interviews were videotaped and the interview tapes were watched and scored by 13 raters independently. SPSS program [Norusis, 1990] was used for analyzing the intra-class correlation using the formula of nested n subjects rated by k raters [Shrout, 1995]. The intra-class correlation coefficients of all ratings items among 13 raters ranged from 0.78 to 0.99 in SAPS and from 0.81 to 0.96 in SANS. The intra-class correlation coefficients of the global ratings of symptom dimensions of the SAPS and SANS ranged from 0.93 to 0.98 and from 0.88 to 0.95, respectively.

In the fieldwork, all interviews were recorded with audiotapes. One-fifth of the interviews were selected randomly and checked for quality monitoring by the data manager. The field interviewers were assigned randomly to check all items of the scored interview schedules. The interviewer who scored the original interview had to clarify any missed or ambiguous scores. A double entry key-in procedure was used to assess for and correct data entry errors.

Formulation of Research Diagnoses

The research diagnoses were made based on DSM-IV criteria. Two board certified research psychiatrists made these diagnoses independently. Both psychiatrists performed the diagnostic assessment based on the guidelines of the SDAS, which was constructed following the DSM-IV criteria for item-to-item checking.

The depressive subtype of schizoaffective disorder was defined using DSM-IV criteria. The essential feature was the concurrent manifestation of major depressive episode and schizophrenia criteria symptoms of positive and/or negative symptoms. The positive criteria symptoms were for a minimum of 2-week duration in the absence of prominent mood symptoms. The criterion of the presence of the mood symptoms had to be for a substantial portion of the total duration based on clinical judgment. As the recruited proband case might have long duration of illness, the substantial portion was defined by the presence of mood symptoms for no less than one-third of the duration of being actively ill and the clinical severity was contributed markedly by the presence of mood symptoms.

The final diagnoses were achieved by integrating the information from the PDA, DIGS, SIS, FIGS, clinical summary, and all available medical records. When the two diagnosticians disagreed, a senior clinical research psychiatrist (H.-G. Hwu) resolved the disagreement by reviewing all data schedules and medical records and, if necessary, a discussion with the field psychiatrist who cared for the patient would be arranged for clarification of the clinical condition. When inadequate information was available to make a diagnosis, the subject was re-interviewed. All efforts were made to avoid false positive schizophrenia diagnoses. The final diagnosis was coded as (1) schizophrenia, (2) schizoaffective disorder, depressive type, (3) other diagnosis, or (4) no mental disorders.

RESULTS

A total of 78 hospitals and/or health centers participated in the TSLS program. There were 27 from the North (including 21 hospitals in or near Taipei), 16 from the Middle area, 14 from the South, 12 from the Kaoping area, 7 from Eastern Taiwan, and 2 from the islands. These hospitals covered nearly all psychiatric services for the severely mental ill in Taiwan (Fig. 1).

A total of 1,371 screening sheets, identifying the families with at least two affected siblings, were collected from the study hospitals. Among 883 potential probands identified for this study, 52 had too few family members. The other 831 families were contacted for this study. Among these, 190 (22.9%) refused to participate, and 34 were excluded. Of these 34, 13 families were excluded because they refused to accept the data collection procedures; 20 families were excluded because either the proband or other affected sibling failed to meet diagnostic criteria after final diagnostic assessment; and one family was dropped because of the death of the parent during the data collection period. With the exclusion of the 34 families, 607 families with at least two siblings affected with schizophrenia were successfully recruited in this study.

The recruitment rate was 38.4% from a theoretical total of 1,582 families, which had at least two affected siblings, calculated based on the epidemiological prevalence of 0.3% of schizophrenia, and familial risk of 3.9% in the first degree relatives of the Taiwanese data. The proband recruitment rate per 10^4 population was 0.4 in Taiwan; 0.2 in the North, 0.4 in the Middle area, 0.4 in the South area, 0.8 in the Kaoping area, 0.4 in the East, and 0.5 from the islands (Fig. 1).

A total of 2,490 subjects [1,283 male, 1,117 female; 1,568 siblings, mean age 35.7 ($\pm$ 8.4) years old; 922 parents, mean age 63.6 ($\pm$ 9.3) years old] participated in the study. Of the 1,568 siblings, 1,258 were affected [795 male, 463 female; mean age 35.2 ($\pm$ 8.1) years old; mean age of onset 22.6 ($\pm$ 6.3) years old], and 310 subjects were unaffected (179 male, 141 female; mean age 37.6 ($\pm$ 9.1) years old). Among the parents, 65 parents were affected [14 male, 51 female; mean age 59.1 ($\pm$ 7.9) years old, mean age of onset 33.1 ($\pm$ 12.1) years old], and 857 parents were unaffected [male 395, female 462; mean age 63.9 ($\pm$ 9.4) years old].

Table I shows the number of siblings and parents available in each family ascertained for this study. The mean pedigree size was 4.1 family members. Among the 607 families ascertained for the TSLS program, 564 (92.9%) had a single affected sib-pair, 41 (6.8%) had three affected siblings, and 2 (0.3%) had four affected siblings. Using the n$-$1 rule, these families contain 654 independent sib-pairs.

Table II shows the distribution of diagnoses of the study subjects. Among 1,258 affected siblings, 1,249 cases (99.3%) met DSM-IV criteria for schizophrenia, and nine cases (0.7%) had schizoaffective disorder, depressive type. Among these 1,258 affected siblings and 65 affected parents, there were also other co-morbid disorders of various kinds. One subject (0.3%) of unaffected siblings and six subjects (0.7%) of unaffected parents received the diagnosis of schizotypal personality disorder.

In SAPS assessment at the time of study, the prevalence of marked degree (rated moderate or more) of severity of the global rating of hallucination, delusion, bizarre behavior, and formal thought disorder were 27.4%, 26.0%, 19.2%, and 25.5% in the affected siblings respectively; and were 11.7%, 19.7%, 14.3%, and 32.2% in the affected parents, respectively.

In SANs assessment at the time of study, the prevalence of marked degree (rated moderate or more) of severity of the global ratings of affect flattering, alogia, avolition/apathy, anhedonia/ asociality, and impaired attention were 34.6%, 34.8%, 50.3%, 52.5%, and 33.5% in the affective siblings, respectively; and were 32.8%, 39.1%, 42.2%, 49.1%, and 40.6%, respectively in the affected parents.

TABLE I. Distributions of Families by Number of Siblings and Parents Ascertained

	Number of parents ascertained		
Numbers of sibs	One [(N = 292), n (%)]	Two [(N = 315), n (%)]	Total [(N = 607), n (%)]
2	0 (0.0)	285 (90.5)	285 (47.0)
3	272 (93.2)	25 (7.9)	297 (48.9)
4	16 (5.5)	4 (1.3)	20 (3.3)
5	2 (0.7)	1 (0.3)	3 (0.5)
6	2 (0.7)	0 (0.0)	2 (0.3)

TABLE II. Final Diagnoses Among the Siblings and the Parents, Respectively, by Their Affection Status for Either Schizophrenia or Schizoaffective Disorder, Depressed Type

	Siblings		Parents	
Diagnosis	Non-affected [(N = 310), n (%)]	Affected [(N = 1,258), n (%)]	Non-affected [(N = 65), n (%)]	Affected (%) [(N = 857), n (%)]
Schizophrenia	0 (0.0)	1,249 (99.3)	0 (0.0)	65 (100.0)
Schizoaffective disorder, depressive type	0 (0.0)	9 (0.7)	0 (0.0)	0 (0.0)
No mental disorder	267 (86.1)	0 (0.0)	759 (88.5)	0 (0.0)
Other diagnoses[a]	43 (13.9)	135 (10.7)	98 (11.4)	1 (1.5)
Schizotypal personality disorder	1 (0.3)	0 (0.0)	6 (0.7)	0 (0.0)
Major depressive disorder	13 (4.2)	29 (2.3)	27 (3.2)	1 (1.5)
Manic episode	3 (1.0)	7 (0.6)	2 (0.2)	0 (0.0)
Schizoaffective disorder (bipolar type)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other non-affective psychotic disorder (delusional disorder, brief psychotic disorders)	0 (0.0)	0 (0.0)	5 (0.6)	0 (0.0)
Alcohol abuse/dependence	16 (5.2)	65 (5.2)	23 (2.7)	0 (0.0)
Drug abuse/dependence	3 (1.0)	46 (3.7)	5 (0.6)	0 (0.0)
Generalized anxiety disorder	2 (0.6)	1 (0.1)	8 (0.9)	0 (0.0)
Panic disorder	2 (0.6)	1 (0.1)	2 (0.2)	0 (0.0)
Phobic disorder	2 (0.6)	2 (0.2)	4 (0.5)	0 (0.0)
Obsessive disorder	2 (0.6)	13 (1.0)	3 (0.4)	1 (1.5)
Dysthymia	2 (0.6)	0 (0.0)	4 (0.5)	0 (0.0)
Dementia (or mental retardation)	2 (0.6)	0 (0.0)	9 (1.1)	0 (0.0)
Other psychiatric disorder (pathological gambling, adjustment disorder, psychosis due to other medical conditions)	2 (0.6)	0 (0.0)	3 (0.4)	0 (0.0)

[a]In the affected group, the data shown were the case number and percentage with co-morbid disorder.

The mean adjusted z scores of the signal detection sensitivity index d′ for the undegraded CPT was −1.72 (± 1.81), −0.41 (± 1.27) in the affected (n = 1002) and unaffected (n = 236) siblings, respectively; and was −1.62 (± 1.94) and −0.75 (± 1.61) in the affected (n = 41) and unaffected (n = 658) parents, respectively. Meanwhile, the mean adjusted z scores of the degraded CPT d′ was −1.95 (± 1.49) and −0.62 (± 1.25) in the affected (n = 959) and unaffected (n = 230) siblings, respectively; and was −1.85 (± 1.34) and −1.12 (± 1.47) in the affected (n = 39) and unaffected (n = 628) parents, respectively.

The WCST, the adjusted z scores of perseverative errors were 1.22 (± 1.91) and 0.50 (± 1.58) in the affected (n = 952) and unaffected (n = 226) siblings, respectively; and were 0.60 (± 2.07) and 0.55 (± 1.79), respectively in the affected (n = 41) and unaffected (n = 604) parents. The adjusted z scores of category achieved were −0.71 (± 0.78) and 0.03 (± 0.97) in the affected (n = 952) and unaffected (n = 226) siblings, respectively; and were −0.37 (± 0.47) and 0.03 (± 0.71), respectively, in the affected (n = 41) and unaffected (n = 604) parents.

DISCUSSION

The TSLS program successfully created an efficient infrastructure in the Taiwanese psychiatry service system to ascertain schizophrenia families and had successfully recruited 607 sib-pair families for genetic linkage study. This TSLS contributes a significant amount of samples to the data bank of the NIMH schizophrenia genetic initiative, which had 478 affected sib-pair families up to now (http://zork.mustl.edu/nimk/sz.html). The blood samples and diagnostic data sent to the NIMH data repositories should be useful for the research community.

The families ascertained were from all of Taiwan, with a proband recruitment rate of 0.4 per 10^4 populations. The range of recruitment rates among all areas of Taiwan was 0.2 to 0.8 per 10^4 populations. The ascertainment rate for Northern Taiwan, where the research headquarters is located, was low, 0.2 per 10^4 populations. This is due to the fact that the previous research work in this geographical area led by the senior researcher (H.-G.Hwu) had already collected 118 schizophrenia families with at least two siblings affected with schizophrenia. This sample could be integrated into this TSLS sample to create a sample size of 725 families in Taiwan for linkage and/or association studies based on Taiwanese sample per se.

This ascertained sample largely represents the patient population of schizophrenia in Taiwan. Based on the prevalence of schizophrenia in Taiwan, it was expected that there might be 1,582 families with at least two siblings affected with schizophrenia. The TSLS project recruited 607 families for the genetic linkage study. The recruitment rate was 38.4%.

The diagnosis of depressive subtype of schizoaffective disorder was included for case recruitment in this TSLS. The manic subtype was excluded as this subtype of schizoaffective disorder was shown to be very similar to bipolar affective disorder in family study [Baron et al., 1982; Kendler et al., 1986; Maier and Lichtermann, 1991; Bertelsen and Gottesman, 1995]. In the process of case recruitment, the clinical impression of depressive subtype of schizophrenia was taken as the potential probands of TSLS. The cases of schizoaffective disorder, depressive type represented only 0.7% of the total sample collected. The reason of the relatively low prevalence of schizoaffective disorder, depressive type in this sample is simply due to the designed process of proband recruitment. The clinical impression of schizophrenia in proband identification was much more emphasized and there was no special intention to collect schizoaffective disorder for this study sample.

In addition to the strength of its relatively large sample size, another important feature of the TSLS sample is its relative ethnic homogeneity. In the TSLS program, the aborigine population was not included in the sampling population. The patients of aborigine were excluded by parental history of lineage in routine evaluation. The history evaluation was supplemented by language and physical appearance. It is not difficult to identify the people of aborigine origin based on physical and facial appearance and the tone of their language. All the collected schizophrenia families of the TSLS program

are of a single Taiwanese Han Chinese ethnicity, which is of value in genetic study.

Neuropsychological data of the CPT and WCST in a subset of the TSLS samples are also of strength of this TSLS study. These CPT and WCST data will be useful for defining specific endophenotype of schizophrenia, which may be helpful for detecting susceptibility genes in linkage analysis and/or association study of risk haplotype, risk single nucleotide mutations for schizophrenia. The performance of CPT and WCST was worse in the affected than in the unaffected subjects of both parent and sibling samples, as shown by the z score adjusted by age, sex, and educations. The unaffected parents tend to have mildly worse performance score, after being adjusted by age, sex, and educations, than the unaffected siblings. This is probably due to the cohort effect or emotional factors influencing the performance of these tests.

In summary, the TSLS demonstrates a successful research strategy in a nation-wide genetic linkage program. This TSLS also showed a successful model for international collaborative research in schizophrenia genetic studies. The TSLS provides a useful resource for the genetic linkage and/or association study of schizophrenia and should help clarify the genetic underpinnings of this disorder through the genome scan of the sample and subsequent follow-up studies.

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