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Chromosomal Abnormalities in Child Psychiatric Patients

To determine the frequency of chromosomal abnormalities in a child psychiatric population, and to evaluate possible associations between types of abnormalities and patient's clinical characteristics, cytogenetic examination was performed on 604 patients. Demographic data, reasons for karyotyping, clinical signs, and other patient characteristics were assessed and correlated with the results from karyotyping. Chromosomal abnormalities were found in 69 patients (11.3%); these were structural in 49 cases and numerical in 20. Inversion of chromosome nine was found in 15 subjects, trisomy of chromosome 21 in 11, and fragile X in five patients. When karyotyping was performed because of intellectual impairment or multiple developmental delay, significantly more abnormalities were found than average; when performed because autistic disorder was suspected, the number of abnormalities was significantly fewer. There were no differences in clinical variables between structural and numerical abnormalities, nor among nine types of chromosomal abnormalities, except that numerical abnormalities and polymorphism were found at a later age, and that walking was more delayed and IQ was lower in patients with Down syndrome. Clinicians should be aware of the possible presence of chromosomal abnormalities in child psychiatric populations; the close collaboration with geneticists and the use of more defined guidelines for cytogenetic investigation are important.

Key Words: *Chromosome abnormalities; Child psychiatry*

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INTRODUCTION

All human behavior is the result of both genetic and environmental factors, but the direct correlation of behavior with genetic constitution is difficult to determine because the behavior of an organism is remote from the elementary actions of genes (1, 2). As genetic vulnerability underlies a number of child psychiatric disorders, the current principal challenge is to locate and identify major genes that may predispose a patient to this vulnerability (3). Because chromosomes bear the vehicles of the genes, one approach to investigating specific genetic involvement in psychiatric disorders is to identify associated chromosomal abnormalities; this may be especially important given its unknown pathophysiology and the probable genetic heterogeneity of major psychiatric illnesses (4). When a particular chromosomal abnormality is involved, candidate genes can be further tested for linkage with the particular disorder (3).

There have been a number of case reports of child psychiatric patients with a variety of abnormal chromosomes and many researchers have studied the relationship between chromosomal abnormalities and child psychiatric conditions such as autistic disorder or mental retardation (3, 5). As phenotype extends more broadly than psychiatric diagnosis, traditional diagnostic distinctions are unlikely to coincide with genetically-defined phenotypic boundaries (6). It is therefore necessary to correlate karyotypes with as many clinical variables as possible. Such a study may enable child psychiatrists to recognize those patients on whom chromosome analyses should be carried out, and may lead to establish general guidelines for karyotyping in clinical practice. It can also show which karyotypes are more closely connected than others to a specific phenotype and provide grounds for further genetic studies.

In this respect, the present study assessed the characteristics of child psychiatric patients in whom cytogenetic examination had been performed because of suspicion of chromosomal abnormalities. It was designed, firstly, to determine the frequency of chromosomal abnormalities in a child psychiatric population, and secondly, to evaluate possible associations between clinical characteristics of patients and types of chromosomal abnormalities.

MATERIALS AND METHODS

Research design

Six hundred and four child psychiatric patients who visited the Division of Child and Adolescent Psychiatry of Seoul National University Hospital underwent cytogenetic examinations. On the basis of clinical features, chromosomal abnormalities were suspected. The clinic, located in central Seoul, draws patients from all areas of Korea and covers patients with a wide range of behavioral, emotional, and developmental problems. The survey period covered 11.5 years, from February 1984 to August 1995. Blood chromosome analyses were carried out in the Laboratory of Cytogenetics, Seoul National University.

All patients were initially seen by a child psychiatrist; a complete history was obtained and they underwent psychiatric examination. Some also underwent electroencephalogram (EEG) and psychological testing, including KEDI-WISC (the Korean version of Wechsler's Intelligence Scale for Children), SMS (the Korean version of Vineland Social Maturity Scale), and BGT (Bender-Gestalt Test).

Information, including demographic data (age and sex) and clinical signs which led to referral for investigation, was obtained from notes taken during genetic consultation, and the principal reasons for karyotyping was classified and coded. There were seven major categories, namely speech delay, intellectual impairment, suspected of autistic disorder, growth retardation (physical), attentional problems, multiple developmental delay (in more than two domains of development), and academic problems.

For those with abnormal chromosomes, additional information was obtained through a review of their psychiatric chart. Psychiatric records were available for all the patients with abnormal chromosomes, and from these we collected information relating to major clinical signs (speech delay, intellectual impairment, problems in social development, multiple developmental delay, growth retardation, academic problems, and attentional problems), other clinical characteristics (a history of convulsion, the presence of physical anomalies, the age at which unassisted walking began), the results of EEG and psychological tests, and primary diagnoses (according to DSM-III, DSM-III-R, or DSM-IV criteria, 7)

Method of karyotyping

For most of the patients, the macromethod (8) was used. For infants from whom a large quantity of blood could not be obtained, the micromethod (9) was used. Venous blood (10 mL) was obtained from each patient and added to sodium heparin, and each specimen was incubated in a culture medium consisting of Ham's F-10 (Gibco), fetal bovine serum (Gibco), phytohemagglutinin M-form (Gibco), and antibiotics (penicillin G, streptomycin). The lymphocyte culture was incubated for 72 hr, and 1-2 hr before the end of the period, was treated with colcemid in order to arrest cell division during metaphase. It was then centrifuged and fixed with Carnoy solution, and dried using the air drying method. In all cases, conventional G-banding involved treatment with trypsin and use of the Giemsa method (GTG). Other appropriate banding techniques were employed when structural abnormalities were suspected. Light microscope ($\times$1,000) was used to examine at least 30 metaphases.

When a special examination to detect fragile sites was requested by referring clinicians, the specimen was also incubated in TC 199 culture media (Gibco), which depletes folic acid (10), for 96 hr, one day longer than in conventional culture. A minimum of 100 metaphases from each specimen was examined for fragile X sites, and the presence of the fragile sites at band q27 on the X chromosome was confirmed by G-banding.

For the nomenclature of human chromosomes, the Paris conference supplement (11) and the international system for human cytogenetic nomenclature (12) were adopted.

Statistical analysis

Cytogenetic and clinical data were coded using a standard protocol and the results were tabulated. SPSS (13) was used for statistical analysis. The frequency of demographic and clinical variables in subjects with or without chromosomal abnormalities was calculated using frequency analysis, and clinical variables among abnormal karyotypes were compared using x^2 test, t-test and ANOVA with post hoc Duncan's multiple-range test (statistical significance: $p=0.05$).

RESULTS

Between February 1984 and August 1995, chromosome analysis of the blood of 9,825 patients was carried out in the Laboratory of Cytogenetics, Seoul National University. Of these 604 (6.15%) had been referred from the Division of Child and Adolescent Psychiatry.

As shown in Table 1, the ages of subjects at the time of cytogenetic examination ranged from one to 18 (mean 5.25) years; 435 (72%) were boys and 168 (28%) were girls. Common reasons of cytogenetic investigation were speech delay (298 cases, 49.3%), low intelligence (42.1%)

Table 1. Comparison of demographic data and reasons for karyotyping between groups with or without abnormal karyotypes

	Total	Normal karyotype	Abnormal karyotype	Positive rate (%)
Number of subjects	604	535	69	11.3
Demographic data				
Average age	5.25	5.18	5.79	
Sex M	435	391	44	
F	169	144	25	
Reasons for karyotyping				
Speech delay	298	268	30	9.7
Intellectual impairment	254	216	38	15.0*
Suspected autistic disorder	169	162	7	4.1*
Growth retardation	83	71	12	14.5
Attentional problems	73	68	5	6.9
Multiple developmental delay	29	20	9	31.0†
Academic problems	8	6	2	25.0

*$p<0.05$, †$p<0.01$ (chi-square test)

and suspicion of autistic disorders (28.0%).

Sixty nine subjects revealed some form of chromosomal abnormality (the positive rate was 11.3%), the presence of which was not related to age or sex. When reasons of chromosome analysis were intellectual impairment or multiple developmental delay, rate of chromosomal abnormalities were found to be significantly higher than average (15.0%, 31.0%, respectively), and when the reason was suspicion of autistic disorder, the positive rate was less than average (4.1%).

As shown in Table 2, common clinical signs of chromosomal abnormal patients were speech delay, intellectual impairment, growth retardation, problems in social development, and so on. Fourteen subjects (20.3%) were

Table 2. Comparison of demographic and clinical variables among numerical, structural and combined chromosomal anomaly groups

	Total	Structural anomalies	Numerical anomalies
Number of subjects	69	49	21
Demographic data			
Average age	5.79	5.17*	7.14*
Sex M	44	35	9
F	25	14	11
Clinical signs			
Speech delay	59	42	17
Intellectual impairment	51	35	16
Growth retardation	19	14	5
Problems in social development	14	11	3
Attentional problems	13	8	5
Multiple developmental delay	13	12	1
Academic problems	5	4	1
Other clinical variables			
History of epileptic convulsion	14	9	5
Presence of physical anomalies	21	14	7
Age of walking in months	20.48	19.22*	23.71*
Results of diagnostic tests			
EEG abnormalities	15	11	4
IQ scores	55.31	62.56	46.00
SQ scores	56.60	69.14	45.63
BGT abnormalities	14	7	7
Primary diagnoses			
Mental retardation	52	36	16
Autistic disorder	10	8	2
Developmental language disorder	7	6	1
ADHD	6	6	0
Functional enuresis	4	3	1

*$p<0.05$, (t-test)

found to have suffered from convulsion and 21 (30.4%) had physical anomalies such as strabysmus, polydactyly, hernia, and imperforate anus. The mean age of beginning to walk was 20.5 months (out of 50 patients with available data). Sixteen patients underwent an intelligence test (KEDI-WISC); their mean was 55.31. Among the 15 subjects whose Vineland SMS data were available, the mean SQ was 56.60. Fifteen underwent BGT, by which in 14 cases (20.3%) suggested organic brain syndrome. EEG findings were abnormal in 15 of 31 subjects (21.7 %). Common primary diagnoses of patients with abnormal chromosomes were mental retardation (75.4%), autistic disorder (14.5%), developmental language disorder, attention-deficit/hyperactivity disorder, and functional enuresis.

When categorizing abnormal karyotypes into the two groups shown in Table 2, structural abnormalities accounted for 49 cases (8.1%) and numerical abnormalities for 20 (3.3%). Those in the latter group were older and began to walk later than those in the former, but otherwise, the two groups showed no differences in sex, clinical signs, history of convulsions, physical anomalies, the results of EEG and psychological tests, or diagnoses.

As shown in Table 3, 17 subjects were found to have inversion, including two in which this was combined with other abnormalities, and 11 subjects had trisomy 21 (Down syndrome). Among specific abnormal karyotypes, patients with polymorphism or other numerical anomalies were older than those with partial trisomy or translocation. Patients with Down syndrome began to walk later than those with partial monosomy or polymorphism, and their IQ was lower than those with polymorphism. Patients with translocation were younger at the time of karyotyping than those with polymorphism and other numerical anomalies. Otherwise, there were no clinical difference among nine specific abnormal karyotypes. The details of the 69 chromosomally abnormal patients are summarized in Table 4.

A special culture for the detection of fragile sites was performed on 268 patients; fragile sites were found in

Table 3. Comparison of demographic and clinical variables among groups of specific abnormal karyotypes

	Total	TRA	PT	PM	INV	MAR	POLY	FXS	DS	ONA
Number of subjects	69	10	4	7	15	3	5	5	11	9
Demographic data										
Average age	5.67	3.60*	3.67*	5.20	5.87	5.33	8.40*	3.80	6.45	7.89*
Sex* M	44	6	2	4	13	1	4	5	5	4
F	25	4	2	3	2	2	1	0	6	5
Clinical signs										
Speech delay	59	10	2	5	13	3	4	5	11	6
Intellectual impairment	51	9	3	4	11	2	2	4	9	7
Growth retardation	19	6	1	2	3	0	2	0	4	1
Problems in social development	14	1	0	2	5	1	2	0	2	1
Attentional problems	13	3	0	1	2	0	2	0	3	2
Multiple developmental delay	13	1	2	2	5	0	0	2	1	0
Academic problems	5	0	0	1	1	0	2	0	0	1
Other clinical variables										
History of epileptic convulsion	14	2	0	2	5	0	0	0	2	3
Presence of physical anomalies	21	5	2	1	2	1	2	1	3	4
Age of walking in months	20.48	24.43	27.00	11.50*	17.58	18.00	15.40*	20.40	27.86*	19.57
Results of diagnostic tests										
EEG abnormalities	15	4	0	0	7	0	0	0	2	2
IQ scores	55.31	none	none	52.67	63.00	68.00	85.00*	none	40.00*	47.00
SQ scores	56.60	52.00	none	68.50	69.00	none	none	5.33	46.33	43.50
BGT abnormalities	14	0	0	1	4	0	1	0	4	4
Primary diagnoses										
Mental retardation	52	8	3	5	13	1	2	4	8	8
Autistic disorder	10	0	0	2	2	1	3	0	1	1
Developmental language disorder	7	3	1	0	1	0	0	1	0	1
ADHD	6	1	1	0	2	0	1	1	0	0
Functional enuresis	4	0	0	0	2	0	1	0	1	0

TRA, translocation; PT, partial trisomy; PM, partial monosomy (deletion); INV, inversion; MAR, marker chromosome; POLY, polymorphism (satellite, heterochromatin); FX, fragile X; DS, Down syndrome; ONA, other numerical anomalies

*$p<0.05$, (ANOVA)

Table 4. Abnormal karyotypes of child and adolescent psychiatric patients

TRA	PT	PM	INV	MAR	POLY	FX	DS	ONA
46,XY,t(1;5)	46,XY,4q+	46,XX,1q-	46,XY,inv(1)	47,XX,+mar (×2)	46,XY,22s+	46,XY,FX, 13%	47,XX,+21 (×6)	45,X
46,XX,t(1;8)	46,XY,11q+	46,XX,5q-	46,XY,inv(5q)	47,XY,+mar	46,XY,14s+ (×2)	46,XY,FX, 15%	47,XY,+21 (×5)	46,XX/45,X
46,XY,t(2;10)	46,XX,18p+	46,XX,18p-	46,XX,inv(9) (×2)		46,XX,16qh+	46,XY,FX, 19%		47,XYY (×2)
46,XY,t(3;6)	46,XY,inv(9),11q+	46,XY,5p-	46,XY,inv(9) (×11)		46,XY,16qh+	46,XY,FX, 22%		47,XXX
46,XX,t(3;10)		46,XY,Yq-				46,XY,FX, 26%		48,XXXX
46,XY,t(7;12)		46,XY/46,XY,10p-						46,X,i(Xq)
46,XY,t(13;20)		45,XY,-21,der(22)t(21;22)(q21.3;p11.2)mat						46,XY/47,XY+18
46,XX,t(8;15)(p12;q26)								47,XXY,inv(9)
45,XY,-22,+der(2)t(2;22)								
45,XX,t(13;14)18p+								

Legend as in Table 3
(×number) is the number of cases

five of whom (1.9%). In cells examined, the rate of fragile site expression varied from 13% to 26%; among such patients, mental retardation was diagnosed in four, and autistic disorder in none.

DISCUSSION

Chromosomal lesions are estimated to affect more than 10% of all conceptions and approximately 0.5 to 1% of all newborns (14-17). The positive rate of chromosomal abnormalities in the present study (11.3%) was lower than in samples referred by pediatric clinics (28%, 18, 28.8%, 19, 17.2%, 20, respectively), but higher than in random psychiatric patients (5.1%, 21). The sex ratio of patients with abnormal chromosomes (9 : 5), lower than that of all patients (3 : 1) may be largely due to the near-equal sex ratio of numerical abnormalities. The finding that structural abnormalities were more frequent in boys than in girls may suggest that boys are more susceptible to structural aberrations.

A variety of developmental problems in speech, intelligence, socialization and physical growth were found to be main clinical reasons for karyotyping. Major disorders diagnosed in our clinic between 1985 and 1995 were autistic disorder, mental retardation, developmental language disorder, and attention deficit hyperactivity disorder, in descending order. In this respect, the reasons for referral were in agreement with the characteristic distribution of patients in our clinic. In a Polish cytogenetic study, common reasons for referral were multiple congenital malformation/mental retardation syndrome, suspicion of sex chromosome abnormality, Down syndrome and reproductive wastage (22).

The most common clinical feature of chromosomal abnormality is intellectual impairment (23) and the prevalence of chromosomal abnormalities among mental retardates has been estimated to be about 13.3% (17). In the present study, the frequency of abnormal chromosomes for the patients referred because of intellectual impairment was significantly higher (15.0%) than the average positive rate. Intellectual impairment was the most common clinical sign (51/69) and mental retardation was the most common diagnosis (52/69) among subjects with abnormal chromosomes.

Studies on chromosomal aberrations in patients with autistic symptoms have reported a greater variety of chromosomal abnormalities than in mental retardates. To date, all chromosomes except 7, 14, 19 and 20 have been reported to be aberrant in autistic patients (5). In the present study, the positive rate of chromosome aberration was the lowest when the reason of karyotyping was suspicion of autistic disorder (4.1%), which is consistent with the frequency in an epidemiological chromosome survey of autism carried out by Ritvo et al. (24) who reported a rate of 4.6%. Among the patients with chromosomal abnormalities, only 14 exhibited problems related to social development, and autistic disorders were diagnosed in only ten patients. Chromosomal abnormality is, therefore, not a major cause of autistic disorder and it is not certain that the characteristic developmental delays and symptoms on which a diagnosis of autism is based are directly related to chromosomal abnormalities. There may, however, exist a subgroup of autistic disorder in which abnormal chromosomes play a certain role in pathogenesis.

There are two main types of chromosomal abnormalities; numerical and structural. Numerical abnormalities are either polyploid or aneuploid; structural abnormalities include partial monosomy (deletion), partial trisomy (du-

plication), translocation, inversion, ring chromosome, marker chromosome, polymorphisms (satellite, heterochromatin), and fragile site (25). Numerical abnormalities are often associated with clinical presentations in which the underlying chromosomal etiology is clearly apparent, whereas structural abnormalities are often more subtle in their clinical presentations (26). But in the present study, the average age at the time of karyotyping was significantly younger in structural abnormalities than in numerical abnormalities (5.17 : 7.14). This finding may reflect population characteristics of our clinic; patients with numerical abnormalities having more prominent dysmorphism might have been screened before they came to child psychiatric clinics.

In the present study, the most common form of abnormal karyotypes was the inversion of chromosomes. In particular, 46XY with pericentric inversion of chromosome 9 was the single most common karyotype. Break point of most of them was inv (9) (p11;q13). As chromosome 9 is known to be highly susceptible to structural rearrangements, pericentric inversion 9 is found frequently in the general population as a paraphysiological variant of a normal karyotype. It is one of the most common structurally balanced chromosomal abnormalities in the human karyotype (30-32); and has also been detected in cases of mental retardation, schizophrenia, personality disorder, congenital malformation, and repeated miscarriage (17, 32-35); its clinical significance, however, remains obscure (4). The direct etiological significance of pericentric inversion in cases of mental retardation does not seem to be high (36), but it may interrupt the function of one or more genes close to break points, and this region might be a potential region of interest for linkage analysis (4, 34). According to Serra et al. (37), the estimated prevalence of inversion of chromosome 9 among newborn infants was 0.85%; Hsu et al. (38) reported that its rate of occurrence ranged from 0.26 to 3.5% in amniotic fluid specimens, with highly significant differences for different ethnic groups, the rate was lowest in Asian populations (0.26%). Some recent Taiwanese and Japanese studies showed frequencies of 1.2% and 1.5% in large normal populations (39, 40). In the present study, the frequency rate of 2.5% (15/604) fell within the range of prevelance of previous studies, but is somewhat higher than the reported figure in normal Asian populations. In patients with chromosomal inversions, who are mostly diagnosed as mentally retarded, we were unable to find any discernable clinical characteristics. Like pericentric inversion of chromosome 9, polymorphism is also considered to be normal variants. In this study, polymorphisms of patients whose parents' karyotyping result were not available were included as abnormal chromosomes.

Down syndrome is the most common chromosomal aberration leading to live birth and the most common individual cause of mental retardation. The present study did not show the reported male excess of about 3:2 or 1.23:1 (25, 41). Kokubun et al. (27) reported that only 11% of children with Down syndrome began to walk within the normal age limit of 18 months, and 33% began after the age of two. The developmental delay in locomotion seen in Down syndrome may be a function of the degree of impairment of associated neuromuscular mechanisms (28).

We identified fragile sites on X chromosomes in five boys among 268 subjects on whom special folate-deficient culture media was utilized. Though family members of the proband were examined cytogenetically, those results were not included in this study. Fragile X is a constriction that appears at band Xq27, and the basis of fragile X syndrome is the expansion of a CGG trinucleotide repeat in the fragile X mental retardation 1 (FMR1) gene (14, 42-44). Molecular technology is known as more precise method to diagnose the syndrome, but it was not used in this study. The prevalence of fragile X syndrome has been estimated to be about 0.1% in males and 0.05% in females (14, 45). In the present study, the prevalence was 1.9%, much lower than the rates reported in a study on 153 mentally retarded boys in Korea, where ten cases (6.5%) showed fragile Xq27 (46), and in a Taiwanese study on 341 mentally retarded children, which found 13 patients (3.8%) with fragile X syndrome (47). Among 105 Chinese children with autistic spectrum disorder, Wong and Lam (48) found fragile X syndromes in two boys (2%). Although a few show autism, an unusual pattern of social avoidance (rather than definite autistic features) is characteristic in such patients (6). In the present study, four boys were diagnosed as mentally retarded; none showed autistic disorder; this result may be due to differences among laboratories in the preparation of cell cultures (media, pH, duration, folate level, etc) and in the scoring and analysis (the number of cells counted, the cut-off percentage of positive cells as the criterion for fragile X diagnosis) (42, 49). The diagnosis of fragile X syndrome is confirmed cytogenetically only if at least 100 metaphases are analysed (50), and the same policy was adopted in our study. Reexamination was performed to confirm the fragile X syndrome if at least one cell in 100 is found to contain fragile X. In our result, every boys with fragile X showed fragile sites more than 13% of cells analysed. Standard technical procedures for identifying fragile X sites have been proposed, but a simple comparison of prevalence rates across various studies has so far proved difficult to show.

All the patients with sex chromosome abnormalities showed low intelligence in the present study. The X

chromosome may be important in cognitive function, and with an increase in sex chromosome complement, the mental retardation is usually increasingly severe (23, 25), it is therefore generally assumed that there is a direct relationship between the number of supernumerary X chromosomes and phenotypic abnormalities and mental retardation (51).

There have been few systematic studies done on the relationship between chromosomal abnormalities and seizure or EEG pattern, although characteristic EEG patterns have been reported in some patients with fragile X syndrome (52) or Angelman syndrome (53). In this study, we were unable to obtain information related to specific types of seizure or EEG patterns.

The failure to find many specific correlations between karyotypes and clinical variables may reflect the genetic and phenotypic heterogeneity that underlies many chromosomal disorders. Seemingly identical genetic lesions can result in highly variable phenotypic expressions. Conversely, markedly different genetic abnormalities can produce essentially identical clinical syndromes (14, 29).

Child psychiatrist often need to make decisions as to when they should consult with geneticists for cytogenetic investigation. Clinical algorithms are needed to help them decide when. In child and adolescent psychiatry, anticipation of future course, an explanation for parents, and medical intervention are potential benefits of cytogenetic examination (54). In the clinical practice of child psychiatry, various findings which may warrant suspicion of chromosomal abnormalities are encountered. These include general developmental delay, idiopathic autism or mental retardation, particularly in those with minor physical anomalies, or a family history of chromosomal abnormalities (23, 26, 55). It has been suggested that the list of indications be enlarged, because in minor abnormalities, some of the classical clinical stigmata may be minimal or lacking (56); in mentally retarded patients, short stature, the presence of microcephaly or hypotonia, and a family history of deaths early in life have been added to the list of indications (14). However, these guidelines need to be modified in accordance with the specific requirements of the clinic and the facilities available (23), and should not be applied rigidly. This study showed that a significant portion of child psychiatric patients have chromosomal abnormalities. It is therefore crucial that in clinical practice, child psychiatrists should be keenly aware of the possible presence of such abnormalities, and should actively collaborate with geneticists.

This study has several methodological limitations, and in evaluating its results, this should be borne in mind. Firstly, we relied exclusively on genetic consultation notes and psychiatric charts. Because information in the notes was usually brief and unorganized, the categorizing of reasons for referral was sometimes not definite. Because the psychiatric record of each patient did not cover all his or her clinical characteristics, much data was missing. This seems to be unavoidable, considering that this study took the form of a retrospective review of notes and charts. Its long duration poses another limitation. Because all the cytogenetic examination during this study period were carried out in the same laboratory, the methods of karyotyping remained unchanged. Several child psychiatrists were involved as diagnosticians, however, and although they all worked for the same clinic, considerable variation in diagnostic practices and referral for cytogenetic study may be expected. Thirdly, the number of patients with chromosomal changes may represent a minimal estimate, and because we used conventional banding techniques and observed only the metaphase, some minor abnormalities might have been overlooked. Greater resolution would allow finer localization of abnormalities and identification of smaller anomalies, and, therefore, the detection of a much greater number of chromosomal aberrations (4, 56). Finally, because the sample size within each abnormality group was small, the statistical results are not wholly reliable as the basis for a definite statement regarding the correlation between specific karyotypes and clinical variables.

In child psychiatry, much more cytogenetic research is needed; the correlation of clinical and chromosomal data from an increased number of subjects might lead to the emergence of more definite associations. A comparative study using two unselected groups, with or without chromosomal abnormalities of children, is desirable; though it is difficult to find such groups, as all children referred for cytogenetic examination are selected (56). In addition, high-resolution and special culture technique should be employed judiciously.

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