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Genetic testing in children with autism spectrum disorders

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Abstract

Objective—The aim of this study was to investigate karyotype abnormalities, MECP2 mutations, and Fragile X in a clinical population of children with Autism Spectrum Disorders (ASD) using The Clinical Report published by the American Academy of Pediatrics.

Methods—Ninety-six children with ASD were evaluated for genetic testing and factors associated with this testing.

Results—Abnormalities were found on karyotype in 9.7% and in DNA for fragile X in 1.4%. Karyotype abnormalities include inv(9)(p12q13); inv(9)(p11q13); inv(Y)(p11q11); Robertsonian translocation (13;14)(8q10q10) and (13,14)(q10q10); 9qh+; Yqh+; 15ps+; deletion 13(p11.2).

Conclusion—Genetic testing should be offered to all families of a child with an ASD, even not all of them would follow this recommendation. Although karyotype and FRAXA assessment will yield almost 10% positive results, a detailed history and physical examination are still the most important aspect of the etiological evaluation for children with ASD. Also, it is important to have geneticists to help in interpreting the information obtained from genetic testing.

Keywords

autism; genetics; child

INTRODUCTION

Autism spectrum disorders (ASD) also known as pervasive developmental disorders are neurodevelopmental disorders characterized by social communication deficits, language disorder and repetitive or stereotypic behaviors or interests.¹ Autism spectrum disorders include DSM-IV diagnosis of autistic disorder, Asperger's Syndrome, and pervasive developmental disorder not otherwise specified. ASD prevalence is 6/1000 and is seen more in males than females.²

There is a significant genetic risk in etiology of ASD³. Population based studies show that multifactorial inheritance involving multiple genes plays an important role.⁴ Risk of having ASD for a sibling of an autistic child is 3–10%.^{5–7} This increases to 33 to 50% if there are two or more siblings having autism.⁸

Physicians such as pediatricians, neurologists and psychiatrists diagnose, and follow-up children with ASD and mostly refer children with ASD to genetic counseling in case of a probable genetic syndrome or dysmorphology. However, most of the children with ASD lack or have subtle dysmorphic features or other medical problems related to a genetic disorder. Therefore, in less than 10% of ASD, there is shown a recognizable comorbid genetic syndrome or medical condition associated with ASD⁴ although it is thought that 30–40% of ASD etiology could be identified with using current genetic testing methods and knowledge.⁹

Genetic counseling can give information to families of children with ASD about the etiology. Finding a genetic reason for ASD provides having needed services, identifying underlying medical risks associated with diagnosis and decreasing morbidity. Family members at-risk of ASD can be tested by recurrence risk consultation. Having a specific diagnosis also prevents unnecessary testing. Because of these reasons, American College of Medical Genetics and Genomics Practice Guidelines On Clinical Genetics Evaluation in Identifying the Etiology of ASD suggest that every person with ASD (and his/her family) should be offered a genetic evaluation.⁹ Also, the American Academy of Pediatrics (AAP) Guidelines on Evaluation of Children with Autism Spectrum Disorders suggests that physicians should consider ordering a G-banded karyotype and Fragile X DNA testing for all children with non-syndromic and intellectually disabled ASD and methyl CpG-binding protein 2 (MECP2) analysis in females who present with regression and autistic features.⁴ By using these guidelines, it was shown that Fragile X syndrome and karyotype abnormalities were seen in up to 2,2% and 6.8% of ASD patients, respectively.^{10–14}

Although a growing body of evidence suggests the potential value of genetic tests for patients with ASD, there is considerable variation in genetic tests ordered by child psychiatrists for the workup of ASD in daily practice. In the present study, our aim was to investigate karyotype abnormalities, MECP2 mutations, and Fragile X in a clinical population of children with ASD to identify the etiology. To our knowledge, this is the first study of routine clinical genetic testing in a Turkish population of ASD.

METHODS

Ninety-six patients diagnosed with ASD having genetic testing were included in this study. This study was done in Autism Center of Excellence at child psychiatry department of Sami Ulus Children's Hospital. The medical records of all children first diagnosed with an ASD between January 2011 and January 2012 were reviewed. Most of the subjects were derived from a previously described Three-item Direct Observation Screen (TIDOS) study.¹⁵ Written consents were obtained from all parents for participation in the study. The diagnosis of an ASD was made through application of a structured *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*) checklist by the authors (PY, OO) who

are all experienced child psychiatrists. Distinction between AD and PDD-NOS was based on presence of full versus subthreshold symptom number in the affected ASD domains according to well recognized *DSM-IV-TR* rules. Also the Social Communication Questionnaire (SCQ), and the TIDOS¹⁵ measures were used. Although 116 charts was identified, 96 children (with pervasive developmental disorder not otherwise specified (PDD-NOS), n=23; and autistic disorder (AD), n=73) had genetic testing completed. Information extracted from the charts included clinical autism diagnosis, sociodemographic characteristics, IQ category (less than 70 or greater than 70), family history of autism, history of regression, presence of dysmorphic features, medical tests ordered, the results of medical tests completed. Most of children (n=83) had cognitive testing completed through varying instruments, including the Vineland adaptive behavior scale, Stanford Binet intelligence scale, Wechsler Intelligence Scale for Children-Revised (WISC-R), and Peabody picture vocabulary test administered by trained staff psychologists. The family history of ASD was taken for parents or siblings and had to have been diagnosed by a physician. The TIDOS measures were completed by the pediatric residents blind to diagnostic status of the subject who were trained in the use and scoring of each observation item. The SCQs were self-administered by parent informants (predominantly mothers) in the clinical setting with help from staff psychologists and residents as requested. The documentation of dysmorphic features was made by a pediatrician. None of the subjects had sensory hearing and/or visual impairments. Genetic tests recorded included karyotype, FRAXA for all cases and MeCP2 DNA for female patients.

Genetic tests

Karyotyping was performed on GTL banded metaphase chromosomes harvested from peripheral blood lymphocytes using standard laboratory procedures, providing a high resolution of approximately 550 bands.

Fragile X test—Isolated DNA was tested by both Southern blot analysis and Polymerase chain reaction (PCR) for the size and methylation status of the CGG repeat expansion within the FMR-1 gene. Southern blot analysis was performed with the probe GLFDig1 on EcoR1 and EagI digested DNA. Primers were Fc, EagU, EagL

MeCP2 DNA mutation analysis—2,3, and 4th exon and exon-intron connecting regions of MECP2 gene which do coding were amplified by PCR, than MECP2 gene sequence analysis was done. Primers were E2, E3, E4a, E4b, E4c/d, E4e. Association of mutations with the disease are controlled from “RettBASE: IRSA MECP2 variation database.

Statistics

Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) 15.0 program was used for statistical analysis. Normality of the distribution of data was evaluated with visual (histograms etc.) and statistical (Kolmogorov-Smirnov and Shapiro-Wilks) tests. For the evaluation of categorical variables, chi-square or Fischer exact t test was used. For multiple comparisons of 5 variables (gender, cognitive skills, dysmorphic features, history of regression, and family history of an ASD) associated with positive genetic testing, a Bonferroni correction was applied, and p<0.01 was accepted significant.

RESULTS

We observed a male to female ratio of 4:1. The mean age at diagnosis was 66.36 months, and the median was 52 months, with a range of 19 to 207 months. ASD clinical subtypes were as follows: pervasive developmental disorder not otherwise specified (PDD-NOS), 24% (n=23); and autistic disorder, 76% (n=73) (Table 1). An IQ test score was recorded for 11 children; WISC-R n=4 (4.2%) and Stanford Binet n=7 (7.3%). Other tests completed were Vineland adaptive behavior scale n=65 (67.7%), and Peabody picture vocabulary test n=8 (8.3%). Because many children did not have a valid IQ test recorded or had cognitive impairment that was too low to be reliably quantified (n=12 (12.5%)), children were assigned to a category of typical cognition or low cognitive level that was based on combined information from an IQ test score (>70 or <70), an estimation of cognitive functioning based on adaptive functions documented in the chart, and abilities recorded. By creating this categorical approach, 64.6% (n=62) of children had cognitive disability in addition to the ASD.

Thirty-five point four % (n=34) had a history of regression. A family history of a sibling with a diagnosis of ASD was present in 4.2 % of subjects (n=4).

The children were categorized into dysmorphic/nondysmorphic based on physical examination. Of the entire sample only 8 patients were reported to have dysmorphic features. Medical characteristics that were recorded included macrocephaly with head circumference >90th percentile in 2 patients. Microcephaly was present in 1 child with a head circumference of <10th percentile. Minor congenital anomalies reported included frontal bossing, syndactily, polydactily, low set ears and hyperpigmented areas.

Genetic testing was completed for 82% of the children for whom the recommendation was made. Out of the 116 children, 96 followed through by obtaining genetic testing of some sort, including 93 who completed karyotype, 72 who had DNA testing for fragile X, and 8 who completed MECP2. The yield of new diagnoses from all genetic testing was only 10% (10 out of 96). There were 9 abnormalities (9.7%) in 93 samples identified on karyotype and 1 Fragile X syndrome (1.4%) in 72 samples. Karyotype abnormalities include inv(9)(p12q13); inv(9)(p11q13); inv(Y)(p11q11); Robertsonian translocation (13;14)(8q10q10) and (13,14)(q10q10); 9qh+; Yqh+; 15ps+; deletion 13(p11.2) (Table 2). Three of 18 girls tested on karyotype were abnormal as 6 of the 75 boys were (1.2%), and the difference in proportions was not significantly different (Fisher's exact test, p=0.369). No significant difference was found on karyotype for children clinically diagnosed with PDD-NOS compared with those clinically diagnosed with autism: Among the 21 children with PDD-NOS, 1 (4.8%) had abnormalities; and among the 72 children with autism, 8 (11.1%) had abnormalities found on karyotype (p=0.678). Also intellectual disability was not associated with a positive yield on karyotype. 8 of 59 children with intellectual disability who had testing recorded had abnormal karyotype (5.7%), whereas only 1 out of 34 (3.3%) of the children with higher cognitive abilities had an abnormal karyotype (p=0.148). 4 of the 34 children with regression had abnormal karyotype reported, whereas 4 out of 56 of those without regression had such findings (p=0.47). Family history did not increase the likelihood

of a positive karyotype. Physical features did not predict a positive karyotype. None of the children with microcephaly or macrocephaly had an abnormality on karyotype.

Out of 61 boys and 11 girls, only 1 was identified with fragile X syndrome (1.4%). This boy had intellectual disability. Testing for Rett Syndrome (MeCP2) was completed on 8 female children and all were normal. Because each of these additional tests had very small numbers, further statistical analysis could not be done.

DISCUSSION

The AAP guidelines have been used since 2007 to examine the yield of genetics evaluation of children with ASD in other countries. Child and adolescent psychiatrists, overall, in Turkey, have not tended to order routine genetic tests although high-resolution karyotype and DNA for fragile X are recommended in all children with ASD. This is the first study to examine the yield of genetics evaluation of children with ASD at a child psychiatry department in Turkey.

The yield of genetic abnormalities in this study was 10%. The yield of karyotype testing alone was 9.7%, which is higher than the rate observed by Wassinka et al.¹¹ of 6.8% in genetic consultation and Shen et al.¹³ of 2.23% in a population study. The yield of fragile X was also at 1.4% in this study and 1.6% in the study by Bailey et al.,¹⁰ but higher than the previously reported value of 0.46.¹³ Higher rates of genetic abnormalities in our study might be result of having a clinical population and ordering genetic tests for all subjects, not only for subjects with a possible genetic disorder. Also, the study of Shen et al.¹³ was a large cohort study, having more high functioning subjects which decrease the possibility of having genetic abnormality.

Although Robertsonian translocations between chromosomes 13 and 14 are seen in ASD patients,¹⁴ it is the most common structural rearrangement in humans and can be seen in people with infertility, miscarriages and mental retardation.¹⁶ Similarly, inversion of chromosome 9, associated with mental retardation and dysmorphic features^{17,18} is also seen in patients with ASD.^{18,19} Abnormalities of chromosomes 13p,²⁰ variation in heterochromatin regions 9qh+^{21,22} and Yqh+¹⁹ are other chromosome abnormalities shown in autistic children or children having autistic features similar to our study. Yqh+ is considered as clinically nonsignificant polymorphism. inv Y is seen in 13.4% of mentally retarded people.¹⁸

There is convincing evidence that “idiopathic” autism is a heritable disorder. In addition, diagnosable medical conditions, cytogenetic abnormalities, and single gene defects (e.g., tuberous sclerosis, fragile X syndrome, and other rare disorders) together account for a considerable part of cases^{23–25}. Evidence from multiplex families with the broader autism phenotypes, together with twin studies, indicates that single-gene defects are rare within families.²⁶ This is a general feature of many genetically influenced complex disorders such as obesity or diabetes. A specific mutation, deletion, or unique set of genetic polymorphisms²⁷ may determine one’s susceptibility of autism, yet even then environmental triggers may modify the phenotypic expression of the disorder.²⁸ A chromosomal anomaly

can be found in a low percentage (less than 5%) of individuals with idiopathic autism.²⁹ A great variety of structural chromosomal abnormalities has been reported in individuals with autism, involving almost all chromosomes and including terminal and interstitial deletions, duplications, inversions, marker chromosomes as well as balanced and nonbalanced translocations.^{30–32}

Most of the chromosomal aberrations seem to be individually unique and we do not know the full implications of them because their relation to phenotype is not established. Balanced chromosomal aberrations occur in a low percentage of healthy individuals, estimated at approximately 1 per 2000 for a de novo reciprocal translocation and 1 per 10000 for a de novo inversion.^{33,34} In 9.7% of our sample, we have found chromosomal aberrations. The incidence of these aberrations in this sample of patients with autism is much higher than expected from the low incidence in the normal population of 1 per 10000 for an inversion and 1 per 2000 for a translocation.^{33,34} This suggests a causal relationship between the chromosomal aberration and the occurrence of autism.

The American College of Medical Genetics recently recommended microarray as the first line evaluation for children with ASD and karyotype or fragile X as second line.⁹ Although CMA reveals more genetic abnormalities,^{14,35} there are difficulties in the interpretation of the results, it is more expensive and access to CMA is more limited, therefore, for routine clinical purposes karyotyping may be more reasonable.

Roesser¹⁴ showed that dysmorphic appearance, lower IQ, and female gender were more likely to have findings on the combined genetic testing. Prospective studies are necessary to examine the phenotypes related to genetic differences, relative genetic yield, cost-effectiveness of etiological evaluation. Child and adolescent psychiatrists, overall, in Turkey, have not tended to order routine genetic tests but high-resolution karyotype and DNA for fragile X are recommended in all children with ASD. As genetic basis of autism is clear but recognizable comorbid genetic syndromes or medical conditions are rare, idiopathic autism is an area that child psychiatrists should take care. Additional test for etiological investigations should primarily be guided by history and clinical examination. This study highlights the need to develop clinical genetic test routine for the workup of ASD cases in Turkey. One of the limitations was having a small sample. Also we didn't do any genetic test to look if the karyotype anomalies were de nova or parentally inherited.

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Table 1**Demographic Summary**

Characteristic	mean $\pm$ sd/n(%)
Age of autism diagnosis in months (range)	52 (19–207)
Male/Female	77 (80.2%)/19 (19.8%)
Autism	73 (76%)
PDD-NOS	23 (24%)
Mother's age in years	32.9 $\pm$ 6.08
Mother's education in years	8.9 $\pm$ 4.5
Father's age in years	36.4 $\pm$ 7.1
Father's education in years	10 $\pm$ 4.4
SES	
Low	54.5%
Medium	25%
High	20.5%
Cognitive skills <70	62 (64.6%)
History of regression	34 (35.4%)
Family history of ASD	4 (4.2%)
Dysmorphic features	8 (8.3%)

PDD-NOS: pervasive developmental disorder not otherwise specified; SES: socio-economic status; ASD: autism spectrum disorder

Table 2

Clinical description of children with positive genetic test

	Diagnosis	Gender	Age (months)	Cognitive testing	Dysmorphic features	Other tests	History of regression
Inversion (9)(p12q13)	Autism	M	24	Vineland score: 20	Nondysmorphic	Fraxa normal	+
Robertsonian translocation (13;14)(8q10q10)	Autism	F	207	Severe intellectual disability	Nondysmorphic	Fraxa normal	-
9qh+	Autism	M	113	Severe intellectual disability	Nondysmorphic	Fraxa normal	+
Yqh+	Autism	M	207	Severe intellectual disability	Nondysmorphic	Fraxa normal	+
Robertsonian translocation (13;14)(q10q10)	Autism	M	35	Severe intellectual disability	Nondysmorphic	Fraxa normal	-
15ps+	PDD-NOS	M	58	AGTE score: 23 months	Nondysmorphic	Fraxa normal	-
deletion13(p11.2)	Autism	F	74	Peabody score:46 months	Nondysmorphic	Rett normal	-
Inversion (Y)(p11q11)	Autism	M	66	Vineland score: 38 months	Nondysmorphic	Fraxa normal	+
Inversion(9)(p11q13)	Autism	F	8	Severe intellectual disability	Nondysmorphic	None	-
Fragile X syndrome	Autism	M	46	Vineland score: 10 months	Nondysmorphic	Karyotype normal	-