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Case Report

A Case of Autism with Ring Chromosome 14

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Abstract

Background: Autism is a complex neuropsychiatric disorder that manifests in early childhood. Although the etiology is unknown yet but, new hypothesis focused on identifying the key genes related to autism may elucidate its etiology. The main objective of the present study was to verify the value of karyotyping in autistic children and identifying association between chromosome abnormalities and autism.

Methods: We examined the peripheral blood lymphocytes cell culture for cytogenetic alterations by GTG-banding technique. The investigation was carried out on 50 autistic patients referred by Pediatric neurologist to Cytogenetic Laboratory in Khorasan-e-razavi Province, Iran.

Results: Using GTG-banding technique, the chromosome analysis of patients identified an unbalanced male karyotype with a r (14) in all 50 metaphases were examined.

Conclusion: Since structural abnormalities may have a critical role in the etiology of autism, according to the region where is affected and number of related genes, therefore an outcome with wide spectrum of clinical manifestations could be expected. Furthermore by considering of recent study, the results indicated that there is an association between chromosome 14 with brain development and neurological disorders, but, in conclusion, it could not be suggested that in order to postulate cytogenetic testing in idiopathic autism patients, specifically screening for chromosome 14 which might has diagnostic value.

Keywords: Autistic disorder, Ring chromosome 14, Cytogenetic analysis

Introduction

Autism spectrum disorders (ASDs) are undoubtedly heterogeneous group of neurodevelopmental disorders with multiple nongenetic and genetic etiology that characterized by impairments in social interaction and communication with stereotyped patterns of behaviors (1) .

Autistic disorder was first described by the psychiatrist Leo Kanner in 1943 (2). Most recently, three subgroups including autistic disorder (AD), Asperger syndrome (AS) and PDD-not otherwise specified (PDD-NOS) are identified (3). Epidemiological studies have shown the prevalence of autism spectrum disorders (ASD) has risen in recent years (4).

ASD has been reported in approximately 1 in 100 children in the US (5).clinically, Autism often remains undiagnosed until the age of 3 years old. Over 70% of subjects with autism have intellectual disability (ID) (6), while epilepsy exists in approximately 20% to 30%. ASD are four times more common in boys than in girls (7). About 10%–20% of individuals with an ASD have a verified genetic basis.

Evidence suggests that three genetic alterations responsible for ASD are including: cytogenetic alterations (less than 5%), copy number variants (CNVs), (10% to 20%), but single gene mutations,

which Identified in a in non-syndromic ASD patients is too low (4).

In 5%–10% of ASD patients, *de novo* events like submicroscopic deletions and duplications affect many different loci in different chromosomes (8). Cytogenetically, ring chromosomes are observed with all human chromosomes (9). It is estimated that 50% of reported ring autosomes are from the acrocentric chromosomes and that ring chromosomes usually result from two terminal breaks in both chromosome arms, followed by fusion of the broken ends, or from the union of one broken chromosome end with the opposite telomere region, leading to the loss of genetic material (10).

Ring chromosome 14 is relatively uncommon chromosome structural abnormalities and first described by Gilgenkrantz (11). A ring chromosome formation of an acrocentric chromosome is often associated with increased severity of clinical symptoms depending on variable amount of the genetic material which is lost (12).

The goal of this study was to identify value of karyotyping in autistic children and determine the necessity of cytogenetic study in ASD patients.

Materials and Methods

We enrolled 50 autistic patients and the inform consent was given from all of them and their parents. These patients were referred by pediatric neurologists and neuropsychiatrists from 2006-2012. In this investigation the patients' age ranged from 4 to 14 years old and the sex ratio of male/female was 3:1. Chromosomal analysis was performed according to standard procedures using GTG-banding. Peripheral blood lymphocytes were cultured in RPMI 1640 medium (Gibco®) enriched with FBS, phytohemagglutinin and L- glutamine. The cells were cultured for 72 hours at 37 °C incubator. Cultures were stopped by adding colcemid solution 2 hours before harvesting, then the cells was exposed to hypotonic solution (KCl 0.075 mol/Lit) fixed with methanol/acetic acid (3:1) (vol/vol). Metaphase chromosome spread was prepared and G-banding with the use of trypsin-Giemsa (GTG) at a resolution of 400 to 550 bands was established. A minimum of 50 metaphases were examined from each patient. Karyotypes were assigned according to the International System of Human Cytogenetic Nomenclature (ISCN) 2005. The study was approved by the research Ethics Committee of Mashhad University of Medical Sciences.

Results

A total of 50 patients were screened for chromosome abnormalities by GTG banding technique at high resolution. Among the fifty clinically autistic children, only in one patient (boy 7 years old), was appeared with ring chromosome 14. The karyotype of patient was 46, XY, r (14) (Fig. 1). But at age of 3-month-old he experienced a seizure and epileptic manifestation which was drug-resistant. The EEG test was abnormal and he had susceptibility to infections. According to his pedigree which is drawn by genetic counselor there was no consanguineous marriage and the age of his mother was 33 when he was born. The abnormal karyotype represented in Fig. 1.

Discussion

Chromosomal abnormalities involvement in pathogenesis of autism is not entirely new(13), so in recent years many investigators focused on genetic pathogenesis of this neurodevelopmental disorder (13), using different techniques such as array CGH and cytogenetic analysis, which indicated that several structural alterations in ASD patients karyotype were evident (14).

Chromosomal rearrangement plays an important role in the etiology of ASD; hence chromosomal abnormalities have provided considerable insight into candidate gene and possible molecular pathways involved in ASD (15). Autism is not a single clinical disorder. The variable phenotype spectrum might be suspected to a polygenic and multi factorial disorder (14), so despite many notable research in neuropsychiatric genetics, there are many questions about ASD remains poorly explained (16).

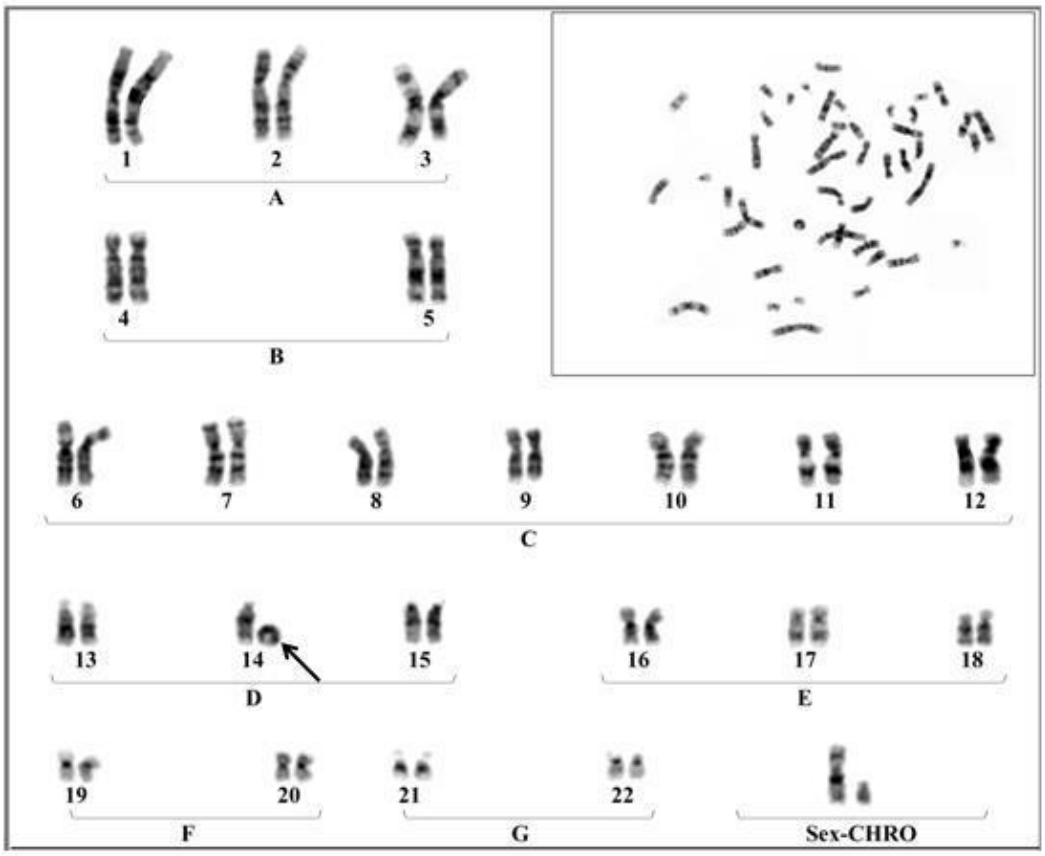

Fig. 1: Karyotype of patient for ring chromosomes 14

The goal of this study was to identify the role of chromosomal abnormalities in the etiology of ASDs and see that whether cytogenetic analysis including GTG-banding technique is useful to identifying autistic children or not, because investigation on autistic children have been previously reported a remarkable variety of chromosomal aberrations which involving almost in all of the chromosomes (1).

Chromosomal alterations which were observable by microscope have been reported in 3-5% of ASD cases (17, 18); the most frequent abnormalities are 15q11–q13 duplications, 2q37, and 22q11.2 and 22q13.3 deletions (19). Rare mutations also have been recognized in NLGN3, NLGN4X (20), SHANK3 (21, 22).Additionally some of ASD suspected genes including Neuroligin, Neurexin and Shank as well as the Fmr1, Mecp2, Ube3a, Nf1, Pten and Tsc1/Tsc2 using of mutant mice has been studied(23). But, until recently, there is no strong evidence supporting direct association between these genes or chromosomal alteration in the etiology of autism**.** But some studies claimed notable association with chromosome 14 abnormalities with some neurological defect including epilepsy, Alzheimer, seizures and CNS developpmental problems in patients with this clinical features (24-27). 1.5 Mb deletions on chromosome 14 in a 14 year old autistic boy as well as observations of a ring chromosome 14 in autistic boy has been reported by Castermans D. et al. study points to putative autism locus on chromosome (14) (28, 29). These observations are comparable to the present study.

Additionally, chromosome 14 deletions is related to language development impairment that is common observation in autistic patients (27). Some point mutations also have been identified in the NRXN1 and NRXN2 genes at 14q24.3-31.1 region that have been implicated in synapse function

(30, 31). On the other hand, it should be noted that some of neurological development related genes such as Presenilin 1 (PSN1) which is involved in the development of the brain and spinal cord and the survival of nerve cells, NPAS3 gene which is involved in schizophrenia and creatine kinase-brain type gene (CKBB) lie on chromosome 14, so it seems that chromosome 14 is implicated in development of central nervous system (32, 33).

In this study, ring chromosome 14 was evident only in one patient out of 50 cytogenetically screened patients, therefore such alteration in ASDs disorders may not be suggested for chromosomal analysis for all of ASD suspected patients, so chromosomal investigation will be recommended only when consanguinity marriage, susceptibility to single gene disease or multifactorial disorder is excluded. However, by considering the result of recent study, which indicate that there is an association between chromosome 14 with brain development and neurological disorders, but, in conclusion, it could not be suggested that in order to postulate cytogenetic testing in idiopathic autism patients, specifically screening for chromosome 14 which might has diagnostic value.

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Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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References

1. Rai V (2011). Autism Genetics and Cytogenetic Abnormalities. *Trend in Molecular Science*, 3 (1): 1-13.
2. Kanner L (1943). Autistic disturbances of affective contact. *Nerves Child*, *2* (3): 217-250.
3. Fombonne E (2004). Epidemiology of autistic disorder and other pervasive developmental disorders. *J Clin Psychiatr*, 66 (10): 3-8.
4. Miles JH (2011). Autism spectrum disorders—a genetics review. *Genet Med*, 13 (4): 278-294.
5. Baio J (2012). Prevalence of Autism Spectrum Disorders: Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. Morbidity and Mortality Weekly Report. Surveillance Summaries. *Centers for Disease Control and Prevention*. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm
6. Yeargin-Allsopp M, Rice C, Karapurkar T, et al (2003). Prevalence of autism in a US metropolitan area. *JAMA*, 289 (1): 49-55.
7. Fombonne E (2009). Epidemiology of pervasive developmental disorders. *Pediatr Res*, *65* (6): 591-598.
8. Geschwind DH (2011). Genetics of autism spectrum disorders. *Trends Cogn Sci*, 15 (9): 409-416.
9. Schinzel A (2001). *Catalogue of unbalanced chromosome aberrations in man*. 2nd ed. Walter de Gruyter, Berlin, pp.: 91-92.
10. Sigurdardottir S, Goodman BK, Rutberg J, et al (1999). Clinical, cytogenetic, and fluorescence in situ hybridization findings in two cases of "complete ring" syndrome. *Am J Med Genet*, 87 (5): 384-390.
11. Gilgenkrantz S, Morali A, Vidailhet M, Saura, Serville F, Fontan D, Moraine C (1984). [The r (14) syndrome. 3 new observations]. *Ann Genet*, 27 (2): 73-8.
12. Rossi E, Riegel M, Messa J, Gimelli S, Maraschio P, Ciccone R, Zuffardi O (2008). Duplications in addition to terminal deletions are present in a proportion of ring chromosomes: clues to the mechanisms of formation. *J Med Genet*, 45 (3): 147-154.
13. Abrahams BS, Geschwind DH (2008). Advances in autism genetics: on the threshold of a new neurobiology. *Nat Genet*, 9 (5): 341-355.

14. Muhle R, Trentacoste SV, Rapin I (2004). The genetics of autism. *Pediatrics*, 113 (5): e472-e486.
15. Folstein SE, Rosen-Sheidley B (2001). Genetics of austim: complex aetiology for a heterogeneous disorder. *Nat Genet,* 2 (12): 943-955.
16. Rutter M (2005). Aetiology of autism: findings and questions. *J Intell Disabil Res*, 49 (4): 231-238.
17. Reddy K S (2005). Cytogenetic abnormalities and fragile-X syndrome in Autism Spectrum Disorder. *BMC Medical Genetics*, 6 (1): 3.
18. Vorstman JAS, Staal WG, Van Daalen E, Van Engeland H, Hochstenbach PFR, Franke L (2005). Identification of novel autism candidate regions through analysis of reported cytogenetic abnormalities associated with autism. *Mol Psychiatr*, 11 (1): 18-28.
19. Miller DT, Shen Y, Weiss LA, Korn J, AnselmI, Bridgemohan C, Wu BL (2009). Microdeletion/duplication at 15q13. 2q13. 3 among individuals with features of autism and other neuropsychiatric disorders. *J Med Genet*, 46 (4): 242-248.
20. Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, Van Maldergem L (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet*, 34 (1): 27-29.
21. Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F (2006). Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet*, 39 (1): 25-27.
22. Moessner R, Marshall CR, Sutcliffe JS, Skaug J, Pinto D, Vincent J, et al. (2007). Contribution of SHANK3 Mutations to Autism Spectrum Disorder. *Am J Med Genet*, 81 (6): 1289-1297.
23. Ey E, Leblond CS, Bourgeron T (2011). Behavioral profiles of mouse models for autism spectrum disorders. *Autism Research*, 4 (1): 5-16.
24. Sorge G, Sorge A (2010). Review Epilepsy and chromosomal abnormalities. *Italian Journal of Pediatrics*, 36 (36) doi:10.1186/1824-7288-36-36.
25. Specchio N, Trivisano M, Serino D, Cappelletti S, Carotenuto A, Claps D, et al (2012). Epilepsy in ring 14 chromosome syndrome. *Epilepsy &Behavior*, 25(4): 585-592.
26. Larner AJ (2011). Presenilin-1 mutation Alzheimer's disease: A genetic epilepsy syndrome? *Epilepsy & Behavior*, 21 (1): 20-22.
27. Zampini L, D'Odorico L, Zanchi P, Zollino M, Neri G (2012). Linguistic and psychomotor development in children with chromosome 14 deletions. *Clin Linguist Phonet*, 26 (11-12): 962-974.
28. Castermans D, Thienpont B, Volders K, Crepel A, Vermeesch JR, Schrander-Stumpel CT, et al (2008). Position effect leading to haploinsufficiency in a mosaic ring chromosome 14 in a boy with autism. *Eur J Hum Genet*, 16 (10): 1187-1192.
29. Griswold AJ, Ma D, Sacharow SJ, Robinson JL, Jaworski JM, Wright HH, et al (2011). A de novo 1.5 Mb microdeletion on chromosome 14q23. 2-23.3 in a patient with autism and spherocytosis. *Autism Research*, 4 (3): 221-227.
30. Vaags AK, Lionel AC, Sato D, Goodenberger M, Stein QP, Curran S, Scherer SW (2012). Rare deletions at the neurexin 3 locus in autism spectrum disorder. *Am J Hum Genet*, 90 (1): 133-141.
31. Gauthier J, Siddiqui TJ, Huashan P, Yokomaku D, Hamdan FF, Champagne NRouleau GA (2011). Truncating mutations in NRXN2 and NRXN1 in autism spectrum disorders and schizophrenia. *Hum Genet*, 130 (4): 563-573.
32. Mariman EC, Schepens J, van Kessel AG, Wieringa B (1987). EcoRI RFLP at the creatine kinase-brain type gene locus (CKBB, chromosome 14). *Nucleic Acids Res*, 15 (13): 5502.
33. Kamnasaran D, Chen CP, Devriendt K, Mehta L, Cox DW (2005). Defining a holoprosencephaly locus on human chromosome 14q13 and characterization of potential candidate genes. *Genomics*, 85 (5): 608-621.