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Identification of Genetic Changes in Individuals Diagnosed with Autism Spectrum Disorder Using Classical Cytogenetic and FMR1 Sizing PCR Methods

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Abstract

Objective: To investigate the role of chromosomal abnormalities and FMR1 gene variations in the etiology of Autism Spectrum Disorder (ASD).

Methods: This clinical study included 80 patients who were referred to the Medical Genetics Department. Chromosome analyses and FMR1 fragment analysis methods were performed on DNA samples of these patients to detect any variations. The obtained data were compared with the literature data.

Results: Eighty individuals were selected for this clinical study. In three patients, chromosomal abnormalities were found. No FMR1 gene defects were found in any of the patients.

Conclusion: Chromosomal abnormalities were found in 3.75% of the patient population. This is compatible with literature data. The FMR1 gene was not found to be associated with etiology. According to these data, it is seen that chromosome analysis still has a valid place in explaining the genetic etiology of autism spectrum disorder

Keywords: Autism Spectrum Disorder, Chromosome Aberrations, DNA Fragmentation

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that begins in early childhood and is characterized by changes in clinical symptoms that can occur with age, persist throughout life, and are associated with cognitive and behavioral disturbances (1). The core features of autism include difficulties in both verbal and nonverbal communication, impairment in social interaction, repetitive stereotypical behavior patterns, language and communication impairments, and restricted interests. In approximately two-thirds of patients diagnosed with ASD, comorbid conditions such as epilepsy (25–30%), gastrointestinal issues (9–70%), motor deficits (79%), attention deficit hyperactivity disorder (ADHD) (around 30%), sleep problems (approximately 50–80%), intellectual disability (45%), anxiety, obsessive-compulsive disorder (OCD), and other comorbidities are observed (2,3,4). Symptoms of ASD typically emerge in children between 18 and 24 months of age, and approximately 30% of them experience a loss of previously acquired skills (regression) (5). The prevalence of ASD is reported to be 30–62 per 10,000 individuals. However, the prevalence increases in developed countries depending on the frequency of diagnosis or living conditions, while it decreases in developing countries (6). The frequency of ASD is higher in males, with a male-to-female ratio of 2:1 to 4:1 (7).

Although ASD has been shown to have a multifactorial etiology, twin studies have demonstrated a strong genetic contribution, with heritability estimated to be approximately 40% to 90% (5). Currently, the genetic etiology is known in approximately 25–35% of cases (8). Although more than 100 genes and genomic regions have been identified, ASD remains genetically complex. Currently, there are two theories to explain the genetic architecture of common complex diseases, including ASD. The first one is the common variant–common disease hypothesis, which suggests that genetic risk is attributed to a high-frequency (minor allele frequency >1%) genetic variant (odds ratio <1.5). In this case, common risk variants collectively contribute to the disease. The second theory is the rare variant–common disease hypothesis, which suggests that genetic risk is primarily explained by rare mutations with significant risk (9). Identifying the monogenic causes and cytogenetic abnormalities of ASD has provided initial insights into its genetic components. Classical karyotyping techniques are estimated to reveal chromosomal

abnormalities in approximately 2–5% of individuals with ASD (10). Major structural chromosomal abnormalities are more commonly observed in cases of ASD when accompanied by associated dysmorphic features. Structural chromosomal changes have been reported for each chromosome, including deletions, duplications, inversions, translocations, and marker chromosomes. Most structural aberrations are rare, and their causal roles in ASD are not clear; however, it is known that a few of them are recurrent anomalies (11). The most commonly observed chromosomal anomalies include duplications of variable sizes in the maternal origin 15q11q13 region, as well as duplications or deletions in the 2q37 region, and deletions in the 22q11 and 22q11.3 regions (12). There is also a database compiling chromosomal abnormalities associated with ASD (13).

Microarray analyses allow for the detection of chromosomal microdeletions and microduplications that are too small to be identified by karyotyping. Recent studies have shown that clinically relevant copy number variants (CNVs) undetected by karyotype analysis were found in 7–14% of patients with idiopathic ASD (4). The most common recurrent ASD-associated CNVs are the 600 kb microdeletions in the 16p11.2 region, identified in approximately 1% of cases (14). Approximately 10% of ASD cases exhibit single-gene disorders such as Fragile X syndrome (FXS), tuberous sclerosis (TSC), and Rett syndrome (5).

Today, microarray testing is recommended as the first step in the algorithm for determining the causes of ASD. However, literature data emphasize that chromosomal anomalies account for approximately 5% of the etiology. Our study aimed to contribute to the understanding of cytogenetic and molecular etiology based on the data obtained in our research. Given the limited number of studies on the genetic factors in cases diagnosed with ASD in our country, we aimed to determine the frequencies of chromosomal anomalies and mutations in the FMR1 gene.

METHODS

Our study included peripheral blood samples from a total of 80 patients who presented to the Department of Child and Adolescent Psychiatry Outpatient Clinic between December 2011 and April 2013 and were diagnosed with Pervasive Developmental Disorder (now referred to as Autism Spectrum Disorder) according to the DSM-V-TR criteria at that time, and were evaluated for dysmorphic features at the Medical Genetics Outpatient Clinic. Patients diagnosed with ASD were initially examined using chromosome analysis from peripheral blood cells obtained from heparinized tubes. In the second stage, the fragment analysis method was used to determine the number of CGG repeats in the FMR1 gene from DNA samples obtained from EDTA tubes. Sterile conditions were maintained for the cultivation of heparinized blood in two separate culture media. The cultures were incubated at 37°C for 72 hours. At the 72nd hour, 0.1 ml of colcemid was added to arrest cells at the metaphase stage during mitosis. After the harvest process (0.075 M KCl solution), the cells were fixed in Carnoy's fixative solution (3 parts methanol to 1 part acetic acid). Subsequently, the cells were spread onto slides and subjected to cytogenetic analysis of metaphase plates using the GTG banding method.

Peripheral blood samples were used to obtain DNA using the Qiagen Extraction Kit (QIAGEN; Hilden, Germany). First, PCR was performed using the Fragile-X Sizing PCR Kit (Abbott; Chicago, Illinois, USA), which includes High GC PCR Buffer, Gender Primers, Fragile X Primers, and TR PCR Enzyme Mix. Subsequently, a clean-up process was carried out, and the samples were loaded onto the ABI 3130 automated capillary electrophoresis device along with Hi-DiTM Formamide and ROX 1000 Size Standard for analysis.

RESULTS

The findings of our study reveal that 80% of the cases included were male, while 20% were female patients. The mean age of the cases was calculated to be 8.89 ± 3.94 years. Structural chromosomal anomalies were detected in 3 (3.75%) out of the total 80 patients. In the analysis performed on all cases using the FMR1 sizing PCR method, repeat numbers above the normal range (<55 repeats) were not detected in peripheral blood samples. The chromosomal anomalies identified in the cases are summarized in **Table 1**.

During the evaluation of the patients included in our study between 2011 and 2013, according to the DSM-V-TR, 56 cases were diagnosed with autistic disorder, 13 with atypical autistic disorder, 5 with Asperger syndrome, 3 with Rett syndrome, and 3 with childhood disintegrative disorder. Additionally, a total of 7 cases were found to have comorbid attention deficit hyperactivity disorder (ADHD) with ASD. The diagnoses and dysmorphic features of the cases with chromosomal anomalies detected in cytogenetic analysis are summarized in Table 2.

Case 1 — Figure 1

In Case 1, during the dysmorphic and physical examination, synophrys and bilateral protuberant polydactyly (operated) were detected. A balanced translocation of 45,XY,rob(13;14) was found in the cytogenetic analysis of this case (**Figure 1**). The chromosomal analysis performed on the parents of the case revealed the presence of the same anomaly in the mother, leading to the diagnosis of a maternal-origin Robertsonian-type translocation.

Table 1. Chromosomal Anomalies Detected Cytogenetically in Cases

Case No.	Chromosomal Anomaly
1	45,XY,rob(13;14)mat
2	46,XX,inv dup del(8)(qter→p23.1::p23.1→p11.2:)
3	46,Y,inv(X)(p22q22)mat

Case 1

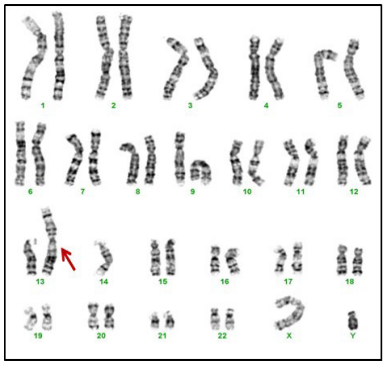
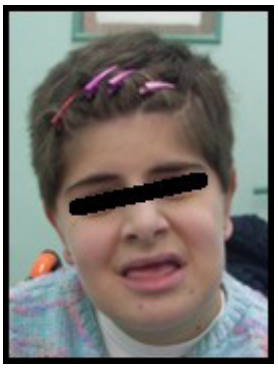


Figure 1



Case 2

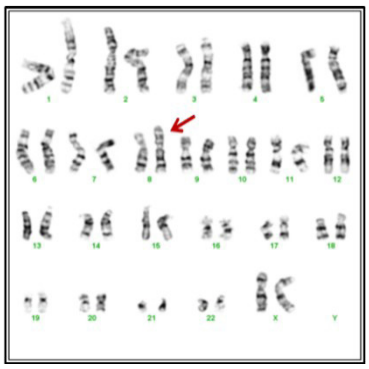


Figure 2

Case 2 — Figures 2 and 3

In Case 35, the dysmorphic and physical examination revealed deep-set eyes, a narrow forehead, a narrow and high palate, prominent ears, clinodactyly of the fifth fingers, kyphoscoliosis, pes varus, and widespread multiple nevi on the skin. Further investigations showed an arachnoid cyst and cerebral atrophy in the left temporal region on cranial CT scan, while cranial MRI revealed a decrease in the thickness of the corpus callosum, accentuation of cerebral sulci, and subcortical atrophy. In the cytogenetic analysis, 46,XX,invdupdel(8)(qter→p23.1::p23.1→p11.2:) was detected (**Figure 2 and 3**).

Case 3 — Figure 4

In Case 48, the dysmorphic and physical examination revealed strabismus, hypertelorism, dysplastic ears, a short philtrum, and a low anterior hairline. The chromosomal constitution of the case was determined as 46,XY,inv(X)(p22.11q22.1) (Figure 4).

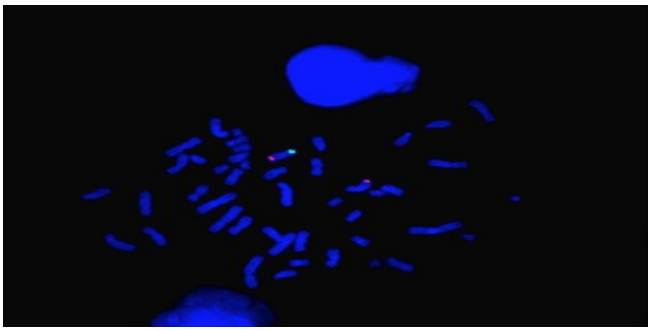


Figure 3

DISCUSSION

Initially, autism spectrum disorder (ASD) was assumed to be environmentally sourced, but a better understanding of the role of genetics soon proved otherwise. It is now understood that ASD is a multifactorial disease involving both genetic and environmental factors, with an estimated 40% to 80% being of genetic origin (15). Early karyotype studies documenting chromosomal abnormalities began to shed light on which regions of the genome were involved. Among the identified genetic causes of autism spectrum disorder, the frequency of chromosomal abnormalities is reported to be around 3–5% (16). These anomalies include balanced or unbalanced translocations, terminal or interstitial deletions, inversions, marker chromosomes, and numerical chromosomal abnormalities. Particularly, chromosomes 15 and X are the most commonly identified chromosomes with anomalies (12). In the extensive study conducted by Xu et al., chromosomal anomalies were reported at a rate of 7.4% (129/1749). Among these 129 chromosomal anomalies, it was found that 17% (22/129) were balanced translocations and inversions (17). In the study conducted by Reddy et al., using conventional cytogenetic methods on a total of 421 patients diagnosed with ASD, chromosomal anomalies were detected in 14 patients (3.33%) (13).

According to the absence of general dysmorphology and microcephaly, autism is divided into two separate groups: essential autism and complex autism (19). Accordingly, all 80 cases included in our study were considered essential autism.

In our study, chromosomal irregularities were detected in 3 out of 80 cases (3.75%), and the frequency of detected chromosomal anomalies is within the rates reported in the literature. One of the cases with anomalies had a balanced chromosomal constitution, while the other two cases had an unbalanced chromosomal constitution.

Case 1: As is known, Robertsonian-type translocations are the most common balanced translocations observed in the general population, with a prevalence of 1/1000 among newborns. Among Robertsonian-type translocations, rob(13q14q) and rob(14q21q) are the most frequently observed types. The balanced translocation rob(13q14q) has indeed been reported as an anomaly in individuals diagnosed with autism spectrum disorder in the literature (20). However, its association with autism spectrum disorder has not been established. The anomaly detected in our study was not considered an

Case 3

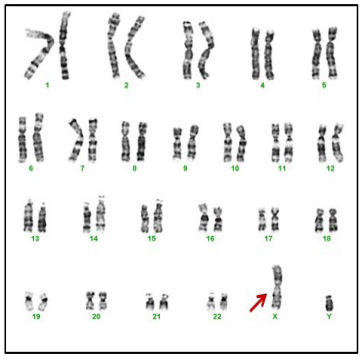


Figure 4

anomaly associated with autism spectrum disorder due to its high frequency in general. However, this study has provided significant benefits by identifying the mother as a carrier of balanced translocation, highlighting the necessity of investigating subsequent pregnancies and evaluating the family from a genetic standpoint.

Case 2: Inverted duplication deletion 8p is a complex chromosomal rearrangement with an estimated prevalence of 1/10,000–30,000 among newborns (22). Most of the time, it arises de novo, but transmission from carrier parents to their children can also be observed. Reorganizations are primarily mediated by two olfactory receptor gene clusters or defensin repeats (ORDRs) at breakpoints; the polymorphic 8p23 inversion between these clusters increases susceptibility to reorganizations on 8p (22).

When looking at the phenotypic characteristics associated with inv dup (8p), the 8p23.2-per region appears to be a critical region associated with autism spectrum disorder (ASD), developmental delay, and impaired language skills. Nucaro et al. reported a case diagnosed with ASD, developmental delay, and epilepsy, where a cytogenetic analysis revealed inv dup del 8p (dup 8p22-p23.1/del 8p23.2-per) (24).

In their study, García-Santiago and colleagues described the clinical features of seven cases with invdupdel(8p) (25). In this study, it was observed that among the seven patients with the same chromosomal constitution, five had agenesis of the corpus callosum and six had variable dysmorphic features. Additionally, minor skeletal anomalies such as clinodactyly were found in all seven patients. Another study attempted to demonstrate the direct phenotypic impact of this chromosomal constitution on ASD (26). It is observed that the clinical findings mentioned in both studies parallel the phenotypic characteristics in our case. In our case, intracranial anomalies including corpus callosum dysgenesis, as well as skeletal anomalies such as clinodactyly and scoliosis, and dysmorphic features are observed.

Glancy et al. reported a duplication in the distal arm of chromosome 8p in a case where the physical examination was normal but speech delay, autism, epilepsy, and learning difficulties were detected. The same anomaly was found in the mother of the case, while the normal chromosomal constitution was reported in the father and male sibling (27). This region includes the ARHGEF10 (OMIM 608236) and CSMD1 (OMIM 608397) genes associated with central nervous system development, the CLN8 (OMIM 607837) gene associated with epilepsy and progressive early-onset epileptic encephalopathy, and the DLGAP2 (OMIM 605438) gene considered a candidate gene for early-onset epilepsy. Hand et al. identified del(8p)/inv dup del (8p) anomaly in mosaic form in a case with a relatively milder phenotype characterized by psychomotor and speech delay. In this case, no dysmorphic features observed in our case were present (28).

Wen-Jun Guo et al. reported seven cases with invdup chromosome anomaly, clinically characterized by minor facial anomalies, mental retardation, microcephaly, growth retardation, seizures, hypotonia, structural brain anomalies, orthopedic anomalies, and kyphoscoliosis. In three of these cases, an additional deletion was found in the 8p telomeric region. Additional clinical findings were not specified in cases where deletion was detected (29). When considering our case along with the literature data, it is thought that the relevant chromosomal anomaly may be associated with pervasive developmental disorder, and further molecular analysis of this region is necessary.

Case 3: Bhat et al. reported the chromosomal constitution of 46,Y,inv(X)(p22.1q13) and 46,X,inv(X)(p22.1q13) in a 7-year-old patient diagnosed with autism spectrum disorder (ASD) who exhibited thickening of the alae nasi and columella, mildly upward slanting palpebral fissures, dysplastic ears, short nose, and a hypotonic facial appearance, as well as in the patient's mother (30). Similarly, Lepretre et al. excluded Fragile X syndrome in a 6-year-old boy presenting with mild dysmorphic features such as retrognathia, prominent forehead, and strabismus, along with behavioral disturbances and intellectual disability. Cytogenetic and molecular analyses revealed a pericentric inversion of the X chromosome similar to the anomaly observed in our case. Both studies suggested that a variation in the IL1RAPL1 gene located at chromosome Xq22.1 could play a role in the etiology. Deletions/mutations in the IL1RAPL1 gene have been reported in some cases of nonsyndromic X-linked mental retardation (31). However, the impact of complete deletions or truncated mutations of this gene in individuals with ASD has not yet been elucidated.

Recent studies have shown the association of the PTCHD1 (patched domain-containing protein 1) gene located in Xp22.11 with ASD and ID (Intellectual Disability). The PTCHD1 gene is primarily expressed in developing and adult brain tissues, with the highest expression observed in the cerebellum (32). Deletions encompassing the PTCHD1 gene have been reported in cases of ASD and ID (33). Additionally, a study involving 900 ASD and 225 ID cases identified seven missense variants in eight families (six ASD and two ID cases) (31). It is noteworthy that in all cases, the affected male probands were inherited from healthy mothers, consistent with an X-linked inheritance model. In a systematic clinical study of 23 individuals with truncating variants or deletions involving PTCHD1, although mild dysmorphic features were reported in some cases, most cases did not exhibit dysmorphic features. The study results indicate that PTCHD1 defects may cause a non-syndromic neurodevelopmental disorder characterized by variable features of autism spectrum disorder and other behavioral symptoms, along with infantile hypotonia and motor coordination issues.

However, a missense mutation in the Synaptotagmin-Like Protein 4 (SYTL4) gene localized at Xq22.1 has been demonstrated in a woman diagnosed with autism spectrum disorder, who did not exhibit skewed X

chromosome inactivation. Also, a maternally inherited missense variant has been associated with autism in a 7-year-old individual diagnosed with ASD (35). Although the inversion observed in our case appears balanced, it could lead to some mutations or deletions in these genes during the formation of breaks. In conclusion, the X chromosome pericentric inversion detected in our case may be associated with pervasive developmental disorders, but further molecular analyses are necessary to confirm this.

FMR1 Gene Fragment Analysis
Autism spectrum disorder with known single-gene disorders accounts for approximately 5% of the etiology. Rett syndrome, Fragile X syndrome, tuberous sclerosis, and Schuurs-Hoeijmakers syndrome are just a few examples, and among these, Fragile X syndrome, which has the highest association, is observed in approximately 1–3% of individuals diagnosed with ASD (36). Tran and colleagues recently demonstrated that mutations in FMRP and FXRP1 may lead to abnormal RNA-regulatory enzyme activity, subsequently causing widespread adenosine-inosine hyporegulation in the brain tissue of individuals with ASD (37).

In the study by Harris et al., 17 out of 63 individuals diagnosed with Fragile X syndrome (27%) were also diagnosed with autism spectrum disorder (38). In the study conducted by Reddy et al. on a total of 433 patients diagnosed with ASD, Fragile X syndrome was diagnosed in 7 out of 316 cases (2.2%) by evaluating the methylation status and repeat expansion of the FMR1 gene using PCR and Southern blot analysis methods (39). In our study, neither premutation nor full mutation was detected in any of our cases.

CONCLUSION

Our results indicate that cytogenetic tests reveal underlying genetic causes, especially in cases with dysmorphic features, while molecular genetic tests targeting the FMR1 gene for Fragile X syndrome are much less common. Our study suggests that in the absence of dysmorphic features, advanced molecular genetic techniques may be more useful for genetic diagnosis in such cases rather than cytogenetic studies.

DECLERATIONS

Ethics Committee Aproval: Study involved publicly available data and did not include human participants or animals, ethical approval was not required.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabi-lities Monitoring Network, 11 sites, United States, 2014. MMWR Surveillance Summ. 2018;67(6):1-23.
3. Meguid NA, Eid MM, Mohamed AM, Ghanoum H, Helmy NA, Eid OM. Contribution of chromosomal abnormalities at 10q and 22q to autism. Res Autism Spectr Disord. 2018;50:43-50.
4. Wiśniowiecka-Kowalnik B, Nowakowska BA. Genetics and epigenetics of autism spectrum disorder—current evidence in the field. J Appl Genet. 2019;60(1):37-47.
5. Lord C, Shulman C, DiLavore P. Regression and word loss in autistic spectrum disorders. J Child Psychol Psychiatry. 2004;45(5):936-955.
6. El-Baz F, Zaghloul MS, El Sobky E, Elhossiny RM, Salah H, Abdelaziz NE. Chromosomal abnormalities and autism. Egypt J Med Hum Genet. 2016;17(1):57-62.
7. Elsabbagh M, Divan G, Koh YJ, et al. Global prevalence of autism and other pervasive de-velopmental disorders. Autism Res. 2012;5(3):160-179. doi:10.1002/aur.239
8. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum di-sorder. Nat Rev Dis Primers. 2020;6(1):5. doi:10.1038/s41572-019-0138-4
9. Liu X, Takumi T. Genomic and genetic aspects of autism spectrum disorder. Biochem Bi-ophys Res Commun. 2014;452(2):244-253. doi:10.1016/j.bbrc.2014.08.108
10. Devlin B, Scherer SW. Genetic architecture in autism spectrum disorder. Curr Opin Genet Dev. 2012;22(3):229-237. doi:10.1016/j.gde.2012.03.002
11. Meyyazhagan A, Balasubramanian B, Bhotla HK, Easwaran M, Shanmugam S, Alagamuthu KK, Pappusamy M. Genetic and cytogenetic screening of autistic spectrum disorder: Ge-notype-phenotype profiles. Meta Gene. 2021;29:100924. doi:10.1016/j.mgene.2021.100924
12. Hogart A, Wu D, LaSalle JM, Schanen NC. The comorbidity of autism with the genomic di-sorders of chromosome 15q11.2-q13. Neurobiol Dis. 2010;38(2):181-191. doi:10.1016/j.nbd.2010.01.001
13. Toronto Centre for Applied Genomics. Autism Database. Available at: http://projects.tcag.ca/autism/. Accessed [insert access date].
14. Fernandez BA, Roberts W, Chung B, Weksberg R, Meyn S, Szatmari P, et al. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11.2 in in-dividuals ascertained for diagnosis of autism spectrum disorder. J Med Genet. 2010;47(3):195-203. doi:10.1136/jmg.2009.069369
15. Chaste P, Leboyer M. Autism risk factors: genes, environment, and gene-environment inte-ractions. Dialogues Clin Neurosci. 2012;14(3):281-292. doi:10.31887/DCNS.2012.14.3.PC
16. Selvi R, Vineeta N, Solomon F, Paul D. Cytogenetics of autism. Sri Ramachandra J Med. 2010;3(2):5-8.
17. Xu J, Zwaigenbaum L, Szatmari P, Scherer SW. Molecular cytogenetics of autism. Curr Ge-nomics. 2004;5(4):347-356. doi:10.2174/1389202043349246
18. Reddy KS. Cytogenetic abnormalities and fragile X syndrome in autism spectrum disorder. BMC Med Genet. 2005;6(1):3. doi:10.1186/1471-2350-6-3
19. Miles JH, Takahashi TN, Bagby S, Sahota PK, Vaslow DF, Wang CH, Hillman RE, Farmer JE. Essential versus complex autism: Definition of fundamental prognostic subtypes. Am J Med Genet A. 2005;135A(2):171-180. doi:10.1002/ajmg.a.30712
20. Medne L, Russell K, Ming J, Krantz I, Souders M, Levy S, Morrissette J. Subtelomeric FISH analysis in 108 autistic patients as an adjunct to chromosome analysis and fragile X testing. Am J Hum Genet. 2003;73(Suppl):Abstract 259.
21. Çöp E, Yurtbaşi P, Öner Ö, Münir KM. Genetic testing in children with autism spectrum di-sorders. Anadolu Psikiyatri Derg. 2015;16(6):426-432.
22. Shimokawa O, Kurosawa K, Ida T, Harada N, Kondoh T, Miyake N, Niikawa N. Molecular characterization of inv dup del (8p): analysis of five cases. Am J Med Genet A. 2004;128A(2):133-137. doi:10.1002/ajmg.a.30043
23. García-Santiago FA, Martínez-Glez V, Santos F, García-Miñaur S, Mansilla E, Meneses AG, et al. Analysis of invdupdel(8p) rearrangement: clinical, cytogenetic and molecular characte-rization. Am J Med Genet A. 2015;167A(5):1018-1025. doi:10.1002/ajmg.a.36850
24. Nucaro A, Pisano T, Chillotti I, Montaldo C, Pruna D. Chromosome 8p23.2-pter: a critical region for mental retardation, autism and epilepsy? Clin Genet. 2011;79(4):394-395. doi:10.1111/j.1399-0004.2010.01623.x
25. Guo WJ, Callif-Daley F, Zapata MC, Miller ME. Clinical and cytogenetic findings in se-ven cases of inverted duplication of 8p with evidence of a telomeric deletion using fluorescence in situ hybridization. Am J Med Genet. 1995;58(3):230-236. doi:10.1002/ajmg.1320580307
26. Fisch GS, Davis R, Youngblom J, Gregg J. Genotype-phenotype

association studies of chromosome 8p inverted duplication deletion syndrome. Behav Genet. 2011;41(3):373-380. doi:10.1007/s10519-011-9447-4
27. Glancy A, Barnicoat A, Vijeratnam R, de Souza S, Gilmore J, Huang S, et al. Transmitted duplication of 8p23.1–8p23.2 associated with speech delay, autism, and learning difficulties. Eur J Hum Genet. 2009;17(1):37-43. doi:10.1038/ejhg.2008.133
28. Hand M, Gray C, Glew G, Tsuchiya KD. Mild phenotype in a patient with mosaic del(8p)/inv dup del(8p). Am J Med Genet A. 2010;152A(11):2827-2831. doi:10.1002/ajmg.a.33673
29. Guo WJ, Callif-Daley F, Zapata MC, Miller ME. Clinical and cytogenetic findings in seven cases of inverted duplication of 8p with evidence of a telomeric deletion using fluorescence in situ hybridization. Am J Med Genet. 1995;58(3):230-236. doi:10.1002/ajmg.1320580303
30. Bhat SS, Ladd S, Grass F, Spence JE, Brasington CK, Simensen RJ, et al. Disruption of the IL1RAPL1 gene associated with a pericentromeric inversion of the X chromosome in a pati-ent with mental retardation and autism. Clin Genet. 2008;73(1):94-96. doi:10.1111/j.1399-0004.2007.00930.x
31. Noor A, Whibley A, Marshall CR, Gianakopoulos PJ, Piton A, Carson AR, et al. Disruption at the PTCHD1 locus on Xp22.11 in autism spectrum disorder and intellectual disability. Sci Transl Med. 2010;2(49):49ra68. doi:10.1126/scitranslmed.3001267
32. Filges I, Röthlisberger B, Blattner A, Boesch N, Demougin P, Wenzel F, et al. Deletion in Xp22.11: PTCHD1 is a candidate gene for X-linked intellectual disability and autism spect-rum disorder. Am J Med Genet A. 2011;155A(11):2802-2813. doi:10.1002/ajmg.a.34278
33. Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, et al. Functional impact of global rare copy number variation in autism spectrum disorders. Nature. 2010;466(7304):368-372. doi:10.1038/nature09146
34. Butler MG, Rafi SK, Hossain W, Stephan DA, Manzardo AM. Whole exome sequencing in females with autism implicates novel and candidate genes. Int J Mol Sci. 2015;16(1):1312-1335. doi:10.3390/ijms16011312
35. Rafi SK, Fernández-Jaén A, Álvarez S, Nadeau OW, Butler MG. High-functioning autism with missense mutations in synaptotagmin-like protein 4 (SYTL4) and transmembrane pro-tein 187 (TMEM187) genes: SYTL4-protein modeling, protein-protein interaction, expres-sion profiling, and microRNA studies. Int J Mol Sci. 2019;20(13):3358. doi:10.3390/ijms20133358
36. Dronca E, Militaru MS, Ciumărnean L, Pop IV. Cytogenetic and fragile X testing in a group of Romanian autistic children. Hum Vet Med. 2015;7(4):276-282.
37. Tran SS, Jun HI, Bahn JH, Azghadi A, Ramaswami G, Van Nostrand EL, et al. Widespread RNA editing dysregulation in brains from autism spectrum disorder patients. Nat Neurosci. 2019;22(1):25-36. doi:10.1038/s41593-018-0287-0
38. Harris SW, Hessl D, Goodlin-Jones B, Ferranti J, Bacalman S, Barbato I, et al. Autism profi-les of males with fragile X syndrome. Am J Ment Retard. 2008;113(6):427-438. doi:10.1352/2008.113:427-438
39. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004;113(5):e472-e486. doi:10.1542/peds.113.5.e472