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Investigation the Relationship of Autism Spectrum Disorder and *FOXP2, GRIN2B, KATNAL2, GABRA4* Genes

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ABSTRACT

Introduction: Autism spectrum disorder is a genetically and phenotypically heterogeneous group. Genetic studies carried out to date have suggested that both common and rare genetic variants play a role in the etiology of this disorder. In our study, we aimed to investigate the effect of *FOXP2, GRIN2B, KATNAL2* and *GABRA4* gene variants in the pathogenesis of autism spectrum disorder.

Method: In our prospectively planned study, all exons and exon-intron junctions of *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes were screened by next generation sequencing analysis in 96 patients who diagnosed with autism spectrum disorder.

Results: In our study, the average age was 10.1 and the male/female ratio was 75/21. Pathogenic or likely pathogenic variants were not detected in *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes, however, 69 intronic variants of unknown clinical significance were detected in 50 cases (52%). Among those, 26 were in the *GABRA4* gene, 22 in the *FOXP2* gene, 13 in the *KATNAL2* gene, and 8 in the *GRIN2B* gene. Twenty three of these 69 variants were novel that were not previously reported in the literature.

Conclusion: In our study, we could not identify a relationship between the autism spectrum disorder and *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes. Identifying genetic risk factors that play a role in the etiopathogenesis of autism spectrum disorder will contribute significantly to understanding the molecular mechanisms of the disease and the development of new treatment strategies. In this context, comprehensive molecular genetic studies such as whole exome or whole genome sequencing are required with higher number of cases in different populations.

Keywords: Autism spectrum disorder, Next generation sequencing, *FOXP2, GRIN2B, KATNAL2, GABRA4*

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INTRODUCTION

Autism spectrum disorder (ASD) affects approximately 1/100 of the population and genetic factors are known to play an important role in the etiology. ASD is a complex neurological disorder characterized by behavioral and psychological problems and repetitive behavioral patterns in children. Patients experience problems in social relations, language development and communication skills. Symptoms are present from early childhood and affect daily activities. Children with ASD diagnosis have higher rates of language problems, intellectual disability, and epilepsy compared to the general population. For ASD, a wide spectrum of behavioral disorders can be categorized under three headings: 1) Social interaction disorder, 2) Language and communication disorder, 3) Areas of interest and activity diversity (1). Intellectual failure, epilepsy, and dysmorphic features may be seen in patients. Children who are followed up with a diagnosis of autism spectrum disorder may develop their speaking and communication skills later on and socialize with their peers at different levels at school age. However, most of these patients require lifelong special education (2).

In studies for the etiology of autism, chromosomal anomalies and molecular pathologies are reported. Some chromosomal anomalies that can be determined by conventional cytogenetic analysis, and various copy number changes that can be observed by molecular methods are associated with autism. Autism clinical findings may also be caused by single gene mutations as in most of the genetic syndromes. ASD has become an important health problem in terms of increasing diagnosis and morbidity rates. Although increasing awareness in medical and social settings is a positive development, the desired levels have not been reached yet. It is important to diagnose autism in the early period, to start education programs early, to increase and enrich the existing skills and to gain new skills, as a result, permanent and significant improvements in the quality of life of patients. Clarifying the etiopathogenesis is of great importance in planning the appropriate treatment, providing genetic counselling related to the course of the disease (3, 4).

10% of ASD cases have single gene defects as seen in other such diseases. It has been reported in many studies that idiopathic autism is of genetic origin. Epidemiological studies report the frequency of autism spectrum disorders with a frequency of 1–2/100 and a male to female ratio of 4–5:1 (5).

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Many studies were conducted with the next generation sequencing technology that has greatly contributed to the understanding of the genetic etiolgy of autism. These studies reported three important clues about the genetic etiology of autism: Rare *de novo* mutations are important in autism genetics, mutant genes encode proteins found in excitatory synapses, and the same mutation in the same gene can lead to different phenotypes (6).

The siblings of the ASD cases have 2–8% increased risk of having ASD compared to the general population. Monozygotic twin studies implicate 60% concordance. Different genetic approaches can be used for ASD diagnosis including whole genome analysis, linkage analysis (in the presence of more than one affected individual in the family), and screening of known causative genes (7–9).

We have decided to screen the *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes in this study, based on their functions in the central nervous system and according to the results of studies reporting a significant relationship with ASD in the literature. To our knowledge, these four genes have been evaluated together in the same ASD study for the first time. Chromosome analysis, array-CGH and Fragile X mutation analysis are routinely performed in patients with ASD in accordance with an algorithm. The genetic etiology could not be clarified when these tests give a negative result. These patients are directed for whole exome or whole genome sequencing analysis which are more expensive and the results can be harder to evaluate. In this study, we aimed to determine the genes that may have a role in the etiology of ASD and the genes which are amenable to screening before exome and genome analysis so that cost-effective and labor friendly genetic tests could be applied. In the light of the results of the whole genome analysis performed in many families, it has been suggested that different genes may play a role in the etiology of ASD. Referring patients with ASD pre-diagnosis from different disciplines (Child and Adolescent Mental Health, Pediatric Neurology, General Child Health and Diseases, Family Medicine, etc.) to the medical genetics clinic will provide important contributions to support and confirm the clinical diagnosis. The genetic tests will contribute to the elucidation of etiopathogenesis and genetic counselling. In our study, we aimed to investigate the relationship between *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes and ASD.

METHOD

Ninety six patients diagnosed with ASD according to DSM-V criteria in the Department of Child and Adolescent Mental Health, Trakya University Faculty of Medicine, were included in our study. Written informed consent forms were obtained from the legal guardians of all cases. For our study, approval of the ethics committee was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee with the decision number of 06/09.

The symptoms of autism were assessed by The Childhood Autism Rating Scale (CARS). Patients had CARS scores above 30 (cut-off for diagnosis of childhood autism), CARS is a 15-item behavior-rating scale designed to detect and quantify symptoms of autism as well as to distinguish them from other developmental disabilities. Each item on the CARS is scored on a Likert scale, from 1 (no signs of autism) to 4 (severe symptoms). The maximum CARS score is 60, and the cut-off for a diagnosis of autism is 30. To assess their attention deficit hyperactivity disorder (ADHD) findings Conners Parent Rating Scale-Revised Short (CPRS-RS) was used.

In our cohort, the results of chromosome analysis, array-CGH analysis and Fragile X analysis showed no pathology. Array CGH was performed using Agilent 4x180K ISCA CGH + SNP Array, testing 170.359 copy number changes located with an average interval of 25.3 kb. Genomic DNA was isolated from 2 ml of peripheral blood sample taken into an EDTA tube using EZ1 DNA Blood 200 µl Kit (Qiagen, Hilden, Germany) and EZ1 Advanced XL (Qiagen, Hilden, Germany) nucleic acid isolation device were used for this purpose. The concentration and purity of the DNA samples were analyzed in NanoDrop (Nanodrop 2000C, Thermo Scientific, USA) and the DNA samples were stored at -20°C.

Specific primers for *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes were designed using NCBI primary blast. Nextera XT Library Preparation Kit was used to generate DNA libraries required for next generation sequencing. The amplicons obtained by polymerase chain reaction were sequenced in Illumina MiSeq (Illumina) after barcoding according to Nextera XT Library Preparation Kit (Illumina) instructions. Variants were determined and analyzed using the Genomize Seq Software (Genomize, Turkey) program from Fastq data obtained using MiSeq Reporter Software. IGV_2.4.8 (http://software. broadinstitute. org/software/igv/) was used for visual analysis of variants. Pathogenicity of variants was evaluated using databases (HGMD, NCBI dbSNP Database, PubMed) and *in silico* analysis methods such as MutationTaster, PolyPhen, SIFT, in line with ACMG-2015 guidelines.

RESULTS

Of the 96 ASD cases, 21.87% (21) were female and 78.12% (75) were male. The mean age of the patients was 10.17 and the age range was between 1–17. With a high range, 87 (90.6%) of 96 cases had a comorbidity. Thirty-six patients had a comorbidity with attention deficit hiperactivity disorder, thirty patients had intellectual disability, sixteen patients had epilepsy and five patients had anxiety disorder with ASD diagnosis.

No pathogenic or likely pathogenic variant was detected in *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes, however, in 50 (52%) cases, a total of 69 intronic variants of unknown clinical significance in these four genes were detected (Table 1). Twenty six of these variants were in *GABRA4*, 22 in *FOXP2*, 13 in *KATNAL2*, and 8 in *GRIN2B* gene. 23 variants were novel which were not previously reported in the literature, and 46 variants were defined in the dbSNP database. *In-silico* analyzes performed to evaluate the pathogenicity of 23 novel variants, and the minor allele frequency was accepted as <0.01.

DISCUSSION

All exons and exon-intron junctions of *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes were screened in 96 ASD patients by targeted sequencing. Pathogenic and/or likely pathogenic variants could not be detected in these genes in our cohort. Various intronic variants with unknown clinical significance were detected in 50 cases, 23 of them were novel.

In recent years, advancements in technology have become an important tool enabling the generation of information about genetic/epigenetic regulatory networks, chromatin structure, nuclear structuring and genome variations. In this study, sequencing analyzes of all exon, exon-intron junctions were performed with the next generation sequencing method in *FOXP2, GRIN2B, KATNAL2* and *GABRA4* genes, and the analysis of the four genes are completed in a short time.

Technological advancements have enabled the identification of a large number of genes that constitute a comprehensive framework to better understand the complexity and heterogeneity of ASD (10). To date, hundreds of ASD genes have been identified with different pathogenic roles in the development of autism. In addition to dominant, recessive and gene-environment mechanisms, polygenic mechanisms in patients with ASD have been investigated more in recent years (11, 12, 13). In studies using targeted gene analysis, several synaptic cell adhesion molecules and other molecules, such as *NLGN3, NLGN4* (14), *NRXN1*

Table 1. Intronic variants of unknown clinical significance detected in our study

Case	GABRA4 gene variations	FOXP2 gene variations	GRIN2B gene variations	KATNAL2 gene variations	dbSNP
1	ENST00000264318.3:c.494+96C>T				rs1264333940
2		ENST00000408937.3:c.1341+95G>A			novel
3				ENST00000356157.7:c.726+298A>G	novel
4			ENST00000609686.1:c.1655-1367G>A		rs919981461
5	ENST00000264318.3:c.494+98C>T				rs1375850828
6	ENST00000264318.3:c.721+1048T>C				rs959718699
6			ENST00000609686.1:c.412-149dupA		novel
7	ENST00000408937.3:c.258+636G>C				rs146008986
8	ENST00000356157.7:c.332+110_332+114delCTGCAinsTTGCG				novel
9	ENST00000264318.3:c.721+1273C>T				rs575429966
9		ENST00000408937.3:c.1845-339T>C			rs558810304
9		ENST00000408937.3:c.1258-71A>C			novel
10	ENST00000264318.3:c.722-1145T>G				novel
11		ENST00000408937.3:c.672+398T>C			rs1026602298
11		ENST00000408937.3:c.1257+499A>G			novel
12	ENST00000264318.3:c.721+849C>A				rs904385057
13		ENST00000408937.3:c.1844+182T>G			novel
14				ENST00000356157.7:c.648+104G>T	rs868704771
15		ENST00000408937.3:c.1844+52T>C			novel
16			ENST00000609686.1:c.2171+475T>C		rs1347932942
17				ENST00000356157.7:c.726+453G>A	rs973729545
18	ENST00000264318.3:c.494+98C>T				rs1375850828
18		ENST00000408937.3:c.258+100A>G			novel
19	ENST00000264318.3:c.87-11_87-10delTT				rs1491165832
20		ENST00000408937.3:c.1258-404C>A			rs568878424
21		ENST00000408937.3:c.1257+783G>A			rs868815969
22		ENST00000408937.3:c.258+444T>A			novel
23			ENST00000609686.1:c.1329-259C>T		novel
24		ENST00000408937.3:c.2079-776T>A			novel
25		ENST00000408937.3:c.334-612_334-609delACAC			novel
25				ENST00000356157.7:c.451-12C>G	rs753840739
26		ENST00000408937.3:c.*201_*205delTTCTT			rs1428369445
27			ENST00000609686.1:c.1010+101G>A		rs1009486080
27				ENST00000356157.7:c.549+316G>A	rs1048953933
28				ENST00000356157.7:c.1374+243G>A	rs1208146139
29		ENST00000408937.3:c.687_695dupGCAGCAGCA (p.Gln232_Gln234dup)			novel
30		NM_148898.4:c.687_695dupGCAGCAGCA (p.Gln232_Gln234dup)			novel
30	ENST00000264318.3:c.1135-284G>A				rs896891365
31				NM_031303.3:c.1158+109G>A	novel
32	ENST00000264318.3:c.875-86T>A				novel
32			NM_000834.5:c.1654+1089_1654+1097delTTTTTTTTT		rs77527098
32	ENST00000264318.3:c.1135-284G>A				rs896891365
33		NM_148898.4:c.-10-616C>T			rs552379438
33	ENST00000264318.3:c.875-86T>A				novel
33	ENST00000264318.3:c.1135-284G>A				rs896891365
34				NM_031303.3:c.1158+339G>A	novel
35				NM_031303.3:c.1159-224C>T	rs1019098597
36	ENST00000264318.3:c.1135-284G>A				rs896891365

continuation of Table 1

36	ENST00000264318.3:c.722-1451C>A						novel
37					NM_031303.3:c.234+298T>G		novel
37	ENST00000264318.3:c.1135-284G>A						rs896891365
37					NM_031303.3:c.996-370_996-369delTCinsAG		rs386802918
37					NM_031303.3:c.73+489G>A		novel
38	ENST00000264318.3:c.273+573A>T						novel
	ENST00000264318.3:c.273+479A>T						novel
39				NM_000834.5:c.411+356C>G			rs542341184
40			NM_148898.4:c.1543+308A>G				novel
41				NM_000834.5:c.1655-1014A>G			rs1037106109
42		NM_148898.4:c.334-603_334-600delCACA					novel
43	ENST00000264318.3:c.875-86T>A						novel
44	ENST00000264318.3:c.273+573A>T						novel
44	ENST00000264318.3:c.1135-284G>A						rs896891365
45	ENST00000264318.3:c.1135-284G>A						rs896891365
46	ENST00000264318.3:c.1135-284G>A						rs896891365
47			NM_148898.4:c.258+634G>C				rs549604838
47	ENST00000264318.3:c.722-1002T>A						novel
48			NM_148898.4:c.1170-68T>C				rs772814187
48	ENST00000264318.3:c.86+79C>T						rs745319657
49	ENST00000264318.3:c.273+479A>T						novel
50			NM_148898.4:c.471+28C>A				rs750342181

GABRA4, gamma-aminobuthyric acid receptor, alpha-4; FOXP2, forkhead box P2; GRIN2B, glutamate receptor, ionotropic, n-methyl-d-aspartate, subunit 2b; KATNAL2, katanin, P60 subunit, A-like protein 2; dbSNP, the single nucleotide polymorphism database.

(15), *CNTNAP2* (16), *SHANK2* (17), and *SHANK3* (18), have been reported to be associated with ASD. Comparative genomic hybridization (CGH) or whole exome sequencing studies have also enabled the identification of some point mutations, small insertions or deletions (19, 20). Several studies have reported about the relationship of ASD and the four genes analysed in this study. *FOXP2* gene mutations have been reported that cause speech and language impairment (21). *FOXP2*, a member of the FOX family and has been shown to be associated with ASD and speech retardation (22). *GABRA4* is a member of the GABA-A receptor family and is involved in neurotransmission in the central nervous system (23). *GRIN2B* is responsible for autosomal dominantly inherited early infantile epileptic encephalopathy and mental retardation (24). Variants and *de novo* mutations in the *GRIN2B* gene have been identified in various neurodevelopmental and psychiatric disorders, including ASD (25). *GRIN2B* is highly expressed in the prenatal period and begins to decrease after birth in mice, suggesting that it plays an important role in neuronal migration and differentiation and synaptogenesis (26). *KATNAL2* is highly expressed in the central nervous system, and associated with ASD has been reported previously (27).

The gender ratios in our study were consistent with the literature; the male: female ratio was 3.57 (75/21) in our cohort and in literature it is reported that the number of boys diagnosed with ASD is higher than girls (28).

The rapid development of genomic testing technology, bioinformatics approaches and artificial intelligence will facilitate genetic testing results and interpretation as they gain more experience in testing patients applying for diagnosis. Due to the clinical heterogeneity and diagnostic uncertainty in ASD, many studies are required to gain more experience in genetic tests and treatment approaches.

There were several limitations of our study in which we used the candidate gene approach to investigate genetic risk factors in ASD. First of all, the candidate gene approach enabled us to analyse only a limited number of genes. Secondly, we could only traced *de-novo* inheritance since all cases were isolated. Thirdly, our cohort had a relatively small sample size. Increasing awareness for the genetic etiology in ASD and related neurobehavioral conditions is a necessity for providing treatment services. Correct diagnosis, correct orientation of the family with correct genetic counselling will increase the quality of life of ASD cases and increase the usefulness of genetic tests for ASD.

CONCLUSION

In 50 of 96 cases included in the study, intronic variants of unknown clinical significance were classified according to ACMG-2015 criteria. Considering that there may be differences in the classification of these variants with unknown clinical significance over time, the variants will be re-evaluated. In our study, the relationship between ASD and the *FOXP2*, *GRIN2B*, *KATNAL2* and *GABRA4* genes could not be established since we could not detect pathogenic or likely pathogenic variants. In order to elucidate the genetic etiopathogenesis associated with ASD, comprehensive molecular genetic studies such as whole exome or whole genome sequencing studies are required in different populations with higher number of cases.

Ethics Committee Approval: For our study, approval of the ethics committee was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee with the decision number of 06/09.

Informed Consent: Written informed consent forms were obtained from the legal guardians of all cases.

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Conflict of Interest: The authors declare that there is no conflict of interest.

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