EXPLORING HIGH AUTISM RISK THROUGH COMMON GENETIC VARIANTS: A CLINICAL REPORT

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Annotation. *Autism is a neurodevelopmental condition marked by difficulties in social interaction and communication, accompanied by restricted interests and repetitive behavioral patterns. It is widely prevalent, has a strong neurobiological basis, and demonstrates substantial heritability. The etiology of autism is multifactorial and heterogeneous, involving a wide range of genetic determinants, environmental exposures, and epigenetic regulatory mechanisms. Progress in molecular genetics, alongside large-scale epidemiological cohort studies, has enabled the identification of specific medical conditions, as well as genes and environmental contributors that are partially or fully implicated in its pathogenesis. These findings, correlated with clinical characteristics, help guide further research, refine clinical prognostic assessments, and support the development of more effective genetic counseling strategies.*
Keywords: *autism spectrum disorder, exon, DNA, rehabilitation.*

ИЗУЧЕНИЕ ВЫСОКОГО РИСКА АУТИЗМА, СВЯЗАННОГО С ОБЩИМИ ГЕНЕТИЧЕСКИМИ ВАРИАНТАМИ: КЛИНИЧЕСКИЙ ОТЧЕТ

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Аннотация. *Аутизм — это нейроразвивающееся состояние, характеризующееся трудностями в социальном взаимодействии и коммуникации, сопровождаемое ограниченными интересами и повторяющимися поведенческими стереотипами. Оно широко распространено, имеет выраженную нейробиологическую основу и демонстрирует значительную наследуемость. Этиология аутизма является многофакторной и гетерогенной, включающей широкий спектр генетических детерминант, воздействия окружающей среды и эпигенетических регуляторных механизмов. Прогресс в области молекулярной генетики, наряду с крупномасштабными эпидемиологическими когортными исследованиями, позволил идентифицировать специфические медицинские состояния, а также гены и факторы окружающей среды,*

частично или полностью вовлеченные в его патогенез. Эти данные, сопоставленные с клиническими характеристиками, помогают направлять дальнейшие исследования, уточнять клинические прогнозы и поддерживать разработку более эффективных стратегий генетического консультирования.

Ключевые слова: *расстройство аутистического спектра, экзон, ДНК, реабилитация.*

OMMAVIY GENETIK VARIANTLAR BILAN BOG‘LIQ YUQORI AUTIZM XAVFINI O‘RGANISH: KLINIK HISOBOT

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Annotatsiya. *Autizm — bu ijtimoiy o‘zaro ta’sir va muloqotdagi qiyinchiliklar bilan tavsiflanadigan neyro-rivojlanish holati bo‘lib, cheklangan qiziqishlar va takroriy xulq-atvor stereotiplari bilan birga keladi. U keng tarqalgan, kuchli neyrobiologik asosga ega va sezilarli merosxo‘rlikni namoyon qiladi. Autizm etiologiyasi ko‘p omilli va geterogen bo‘lib, keng spektrdagi genetik determinantlar, atrof-muhit ta’siri va epigenetik regulyator mexanizmlarni o‘z ichiga oladi. Molekulyar genetika sohasidagi yutuqlar, shuningdek, keng ko‘lamli epidemiologik kohort tadqiqotlari, uning patogenezida qisman yoki to‘liq ishtirok etuvchi ma’lum tibbiy holatlar, shuningdek, genlar va atrof-muhit omillarini aniqlash imkonini berdi. Ushbu ma’lumotlar klinik xususiyatlar bilan solishtirilganda, keyingi tadqiqotlarni yo‘naltirish, klinik prognozlarni aniqlashtirish va samaraliroq genetik maslahat strategiyalarini ishlab chiqishni qo‘llab-quvvatlashga yordam beradi.*

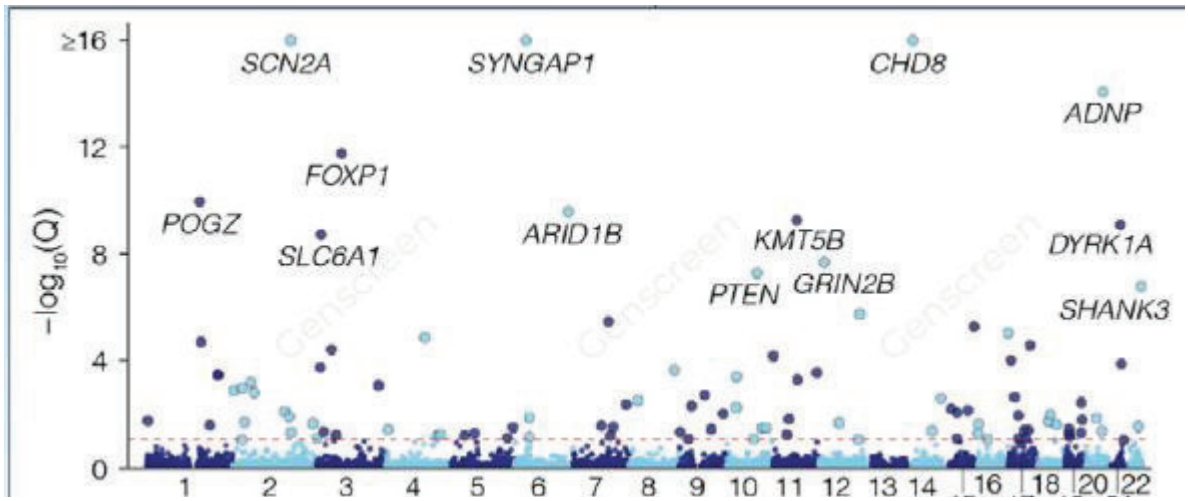
Kalit so‘zlar: *autizm spektri buzilishi, ekzon, DNK, reabilitatsiya.*

Introduction.

More than 100 genes linked to ASD have now been identified. Genetic factors are generally categorized into monogenic and multifactorial causes. Genome-Wide Association Studies (GWAS) compare the frequencies of hundreds of thousands of common genetic variants—Single Nucleotide Polymorphisms (SNPs, occurring in more than 5% of the population)—between affected individuals and controls. Yet, SNPs represent only a small fraction of the total genetic variation, which explains the low heritability estimate for autism based on polymorphisms (0.118). Consequently, the cumulative contribution of these common variants currently lacks prognostic utility. GWAS findings nonetheless indicate that both common and rare variants shape the genetic architecture of autism. In contrast to GWAS outcomes, research on rare genetic variants (frequency <1% in the population) has been markedly more informative, as such variants usually exhibit significantly larger effect sizes compared to common polymorphisms.

Rare variants predominantly consist of copy number variations (CNV) and single nucleotide variants in specific genes, while non-monogenic causes such as trinucleotide repeat expansions, epigenetic changes in DNA structure (ring chromosome), and methylation disorders are less frequently detected. In-

dividual variants may be inherited from a parent or may originate de novo, when the variant initially arises in the parental germline (egg or sperm cells) or later after fertilization, known as post-zygotic somatic variants. There are several observations within these studies of rare variants among people with autism. Rare variants are much more frequently found in autism compared to common variants. In clinics where the cohort includes only patients rather than the general population, the detection rate of rare variants reaches 10–40% among people with autism.



Picture 1. **Results of the study of genes associated with ASD**

Patient M., 4 years old, born in 2020. Parents sought medical advice complaining that the child does not speak, does not respond to their name, and does not play with other children. The child was examined by a neurologist, geneticist, and psychiatrist at the Republican Psychoneurological Hospital named after U.K. Kurbanov. The child was recommended to undergo genetic testing in the form of whole-exome sequencing. The patient's DNA analysis was performed using next-generation sequencing technology, with paired-end reads (2x150 bp) and an average coverage of the target regions of 152x.

The methodology of selective capture of coding regions of DNA of the "whole" exome was used for sample preparation. The standard HGVS nomenclature was used for naming the identified variants. Bioinformatics calling and filtering of sequencing results were carried out using the GATK software in accordance with the recommendations of the BROAD Institute.

Annotation of the identified variants was performed for all known transcripts of each gene from the RefSeq and Locus Reference Genomic databases using a number of pathogenicity prediction algorithms (SIFT, PolyPhen2, PROVEAN, fathmm-MKL), as well as methods for calculating the evolutionary conservation of positions (GERP, PhyloP).

Population frequencies of the identified variants were assessed using data from the Exome Aggregation Consortium, Genome Aggregation Database, Exome Variant Server, and 1000 Genomes Project. For assessing the clinical relevance of the identified variants, databases such as dbSNP, ClinVar, OMIM, HGMD, DMDM, LOVD, and literature data were used. Only variants potentially related to the patient's clinical manifestations were included in the conclusion. Variants classified by various criteria as neutral were not included in the conclusion. The full list of identified variants and sequencing data may be provided upon request to the attending physician.

Material and methods of research

This method has limitations and does not include the study of non-coding regions. The method is not intended for assessing methylation levels, detecting chromosomal

rearrangements (translocations, insertions, deletions, duplications, and inversions of more than 10 base pairs in coding regions of genes), aneuploidy and polyploidy, detecting mosaic mutations, or analyzing repeat length variations (including triplet expansions).

During whole-exome sequencing of the proband, the following nucleotide variants were identified:

Pathogenic variants

Pathogenic Variants: Gene	Position (GRCh37/hg19)	Genotype	Exon	cDNA Variant (AA)	Allele Frequency*	Reference Sequence	Read Depth**
SHANK2	shr17:g.80899344C>T	Heterozygous	40	АК	0.00000120	NM_914114.5	95B

Variants of unknown clinical significance

Variants of Uncertain Clinical Significance (VUS): Gene	Position (GRCh37/hg19)	Genotype	Exon	cDNA Variant (AA)	Allele Frequency*	Reference Sequence	Read Depth**
TBCD	chr17:g.80899345C>T	Heterozygous	38	c.3550C>T (p.Gln1184Ter)	0.00001189	NM_005993.5	189x

Asymptomatic heterozygous carrier status

Asymptomatic Heterozygous Carrier Status: Gene	Position (GRCh37/hg19)	Genotype	Exon	cDNA Variant (AA)	Allele Frequency*	Reference Sequence	Read Depth**
FREM1	chr9:g.14746465TC>T	Heterozygous	36	c.6139del (p.Asp2047fs)	0.00000124	NM_144966.5	64x
IFT140	chr16:g.1570015del2	Heterozygous	29	c.3905_3906del (p.Lys1302fs)	н/д	NM_014714.4	438x

*Allele frequencies are provided according to the samples of conditionally healthy volunteers from the Genome Aggregation Database project (gnomAD v4, more than 807,000 individuals). n/a = no data (not described) ** The number of independent reads of the genome region containing the nucleotide sequence variant.

Interpretation of the Study Results

A comprehensive search for pathogenic and likely pathogenic variants across all cod-

ing regions of the genome was conducted using the proband's DNA sample. Next-generation sequencing revealed a nucleotide substitution, c.3550C>T, located in exon 38 of the TBCD gene (chr17:g.80899345C>T; rs754168355) in a heterozygous state. This alteration introduces a premature stop codon at amino acid position 1184 (p.Gln1184Ter).

The TBCD gene encodes tubulin-specific chaperone D, a protein essential for neuronal morphogenesis. Pathogenic or likely pathogenic variants in this gene—when present in the homozygous or compound heterozygous state—are associated with Early-onset Progressive Encephalopathy with Brain Atrophy and Thin Corpus Callosum (OMIM: 617193), consistent with an autosomal recessive inheritance model. The detected c.3550C>T variant has previously been documented in homozygous and compound heterozygous states in an individual diagnosed with ASD (PMID: 31240573). It is also present in the gnomAD reference population at a frequency of 0.001189% (19 occurrences among 1,598,362 control chromosomes) and has not been observed in a homozygous state.

This substitution leads to the generation of a premature stop codon (p.Gln1184Ter), likely resulting in nonsense-mediated mRNA decay. Therefore, computational tools for pathogenicity prediction are not applicable for this type of variant.

Conclusions

Given the currently available evidence, the heterozygous c.3550C>T (p. Gln1184Ter) variant in the TBCD gene should be classified as a variant of uncertain clinical significance (VUS). A detailed correlation of this molecular finding with the proband's clinical phenotype is necessary for further interpretation. No second pathogenic or likely pathogenic variant in the TBCD gene was identified. Variant assessment was performed according to the guidelines of ACMG, Sherlock, and expert recommendations in clinical genetics and bioinformatics.

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