



THE HIGHEST GENETIC RISK OF AUTISM ASSOCIATED WITH COMMON VARIATIONS – A CLINICAL CASE

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ABSTRACT

Autism is a neurodevelopmental disorder characterized by impairments in social interaction and communication, associated with restricted interests and stereotyped behavior. It has a high prevalence in the population, neurobiological foundations, and high heritability. Its etiology is heterogeneous, with numerous genetic factors, environmental influences, and epigenetic mechanisms recognized. Advances in molecular genetics, as well as epidemiological studies of large cohorts, have made it possible to identify specific medical conditions, as well as genes and environmental factors partially or fully associated with their pathogenesis. This knowledge, in accordance with clinical characteristics, allows for directing further research, drawing conclusions about clinical prognosis, and focusing on genetic counseling.

Genetic Factors

Currently, more than 100 genes associated with ASD have been identified. To date, genetic causes are divided into monogenic and multifactorial. Genome-Wide Association Studies (GWAS) include comparing the frequencies of hundreds of thousands of common gene variants, known as Single Nucleotide Polymorphisms (SNP; frequency >5% in the population), in cases and controls. However, SNPs cover only a very small portion of the overall genetic variability, resulting in a low heritability of polymorphisms for autism (0.118), and the overall genetic predisposition currently has no prognostic value. GWAS results highlight that both common and rare variants contribute to the genetic architecture of autism. Unlike GWAS results, studies of rare genetic variations in autism (frequency <1% in the population) have so far yielded much more discoveries, as they generally show a greater effect size compared to 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. Individual 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.

Patient M., 2 years old, born in 2022. 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.

Method Limitations

The 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	AK	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.14746465T C>T	Heterozygous	36	c.6139del (p.Asp2047fs)	0.00000124	NM_144966.5	64x
IFT140	chr16:g.1570015del	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 search for pathogenic and likely pathogenic variants in all coding regions of the genome was performed in the DNA sample of the proband.

During next-generation sequencing, a nucleotide sequence variant c.3550C>T was identified in exon 38 of the TBCD gene (chr17:g.80899345C>T; rs754168355) in a heterozygous state, leading to the formation of a stop codon at position 1184 of the protein chain (p.Gln1184Ter).

The TBCD gene encodes the tubulin-specific chaperone D protein, which is involved in neuronal morphogenesis. Pathogenic and likely pathogenic variants in the homozygous and compound heterozygous state in the TBCD gene are associated with the development of Early-onset Progressive Encephalopathy with Brain Atrophy and Thin Corpus Callosum (OMIM: 617193), suggesting an autosomal recessive inheritance pattern.



The identified variant c.3550C>T was previously described in the homozygous and compound heterozygous state in a patient with ASD (PMID: 31240573), and is found in the gnomAD control sample with a frequency of 0.001189% (19 occurrences in 1,598,362 control chromosomes; not registered in the homozygous state).

The c.3550C>T nucleotide substitution results in the formation of a premature stop codon p.Gln1184Ter and nonsense-mediated mRNA decay. Pathogenicity prediction algorithms are not applicable in this case.

Based on the available data, the identified variant c.3550C>T (p.Gln1184Ter) in the heterozygous state in the TBCD gene should be classified as a variant of unknown clinical significance. Thorough comparison of the obtained genotype with the clinical data of the proband is required.

A second potentially significant variant in the TBCD gene was not detected during the conducted study.

Variant classification was carried out in accordance with the recommendations of ACMG, Sherloc, and the group of leading experts in the field of genetics and bioinformatics.

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