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A Unique Observation of A Patient With Vulto-Van Silfhout-De Vries Syndrome

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Abstract: Introduction: VULTO-VAN SILFHOUT-DE VRIES SYNDROME (VSVS;OMIM#615828) is an extremely rare hereditary disease associated with impaired intellectual development and speech, delayed psychomotor development and behavioral anomalies, including autistic behavioral traits and poor eye contact. To date, 27 patients with VSVS have been reported in the world literature.

Materials and Methods: We describe a 23y.o. male patient with autism spectrum disorder (ASD) who was admitted to the gastroenterological hospital with signs of pseudomembranous colitis. ASD was first noted in the patient at the age of 2.5y.o. Later he developed epileptic seizers and prominent growth retardation. Prior to the hospitalization he was excluded chromosomal aberrations, Martin-Bell syndrome, aminoacidopathies/aminoacidurias associated with ASD. Whole genome sequencing was prescribed to the patient at 23y.o.

Results: The patient appeared to be a heterozygous carrier of "de novo" variant c.662C>T (p.S221L) in ex 4 of the *DEAF1* gene. c.662C> T had not been previously described in genomic databases. According to the ACMG criteria this missense variant was considered to be pathogenic. VSVS was diagnosed in the patient.

Conclusions: The phenotype of the patient is very similar to the data presented in the world literature. However, growth retardation and cachexia, not previously described in the articles, are of interest.

Keywords: VULTO-VAN syndrome; *DEAF1;* VSVS

INTRODUCTION

VULTO-VAN SILFHOUT-DE VRIES SYNDROME (VSVS; OMIM# 615828) is an orphan disease with an autosomal dominant type of inheritance, associated with impaired speech and intellectual development, delayed psychomotor development and behavioral anomalies, including autistic behavioral traits and poor eye contact.

VSVS was first described by A.T. Vulto-van Silfhout (Netherlands) in 2014 for 4 patients with delayed psychomotor and intellectual development with totally absent or impaired speech [1]. Currently, 27 cases of VSVS have been reviewed in the world literature.

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In addition to psychomotor abnormalities, most patients have additional nonspecific signs, such as hypotension, gait disorders, seizures, that may be refractory, high pain threshold and sleep disorders [2].

VSVS occurs as a result of pathogenic germline mutations in the *DEAF1* gene, which encodes the Deformed epidermal autoregulatory factor-1 (DEAF1). The *DEAF1* gene is located on the short arm of chromosome 11 (11p15.5) and contains 12 coding exons. The product of the *DEAF1* gene, the DEAF1 protein, is represented by several functional domains and acts as a transcription factor in the processing of RNA from the DNA matrix. DEAF1 is involved in the regulation of multiple genes, showing high expressive activity in brain tissues, which explains its key role in the early development of the fetal central nervous system [3].

In most cases, mutations in the *DEAF1* gene are represented by "de novo" missense variants in evolutionarily conserved amino acids of the central SAND domain (a Sp-100, AIRE, NucP41/75, and DEAF1), which is involved in the TTCG- binding of DNA motifs. (**Fig.1**). In vitro functional analysis demonstrated that single-nucleotide substitutions of the SAND domain cause DEAF1 to lose its ability to repress its own promoter, leading to the production of a protein with significant impairment or complete absence of DNA binding ability and transcriptional activity [1]. Variants of the *DEAF1* gene in homozygous and compound-heterozygous state are described in the SAND domain, in the region of the acceptor splicing site, the MYND domain (a myeloid translocation protein 8, nervy, and DEAF1). Some variants in heterozygous state were identified in the functional domains ZnF (a zinc finger motif), NLS (a nuclear localization signal) and between them. These variants have different effects on the functional activity of the protein [4, 5, 6]. Assessment of phenotypic-genotypic correlation showed no significant differences between heterozygous or homo- and compound-heterozygous mutation carriers, except for the presence of microcephaly in carriers of biallelic pathogenic variants in the *DEAF1* gene. The overall spectrum of detected variants of the *DEAF1* gene is described in **Fig. 1** (adapted from: De novo and biallelic *DEAF1* variants cause a phenotypic spectrum/Maria J. Nabais Sá, MD, PhD. GENETICS in MEDICINE) [7].

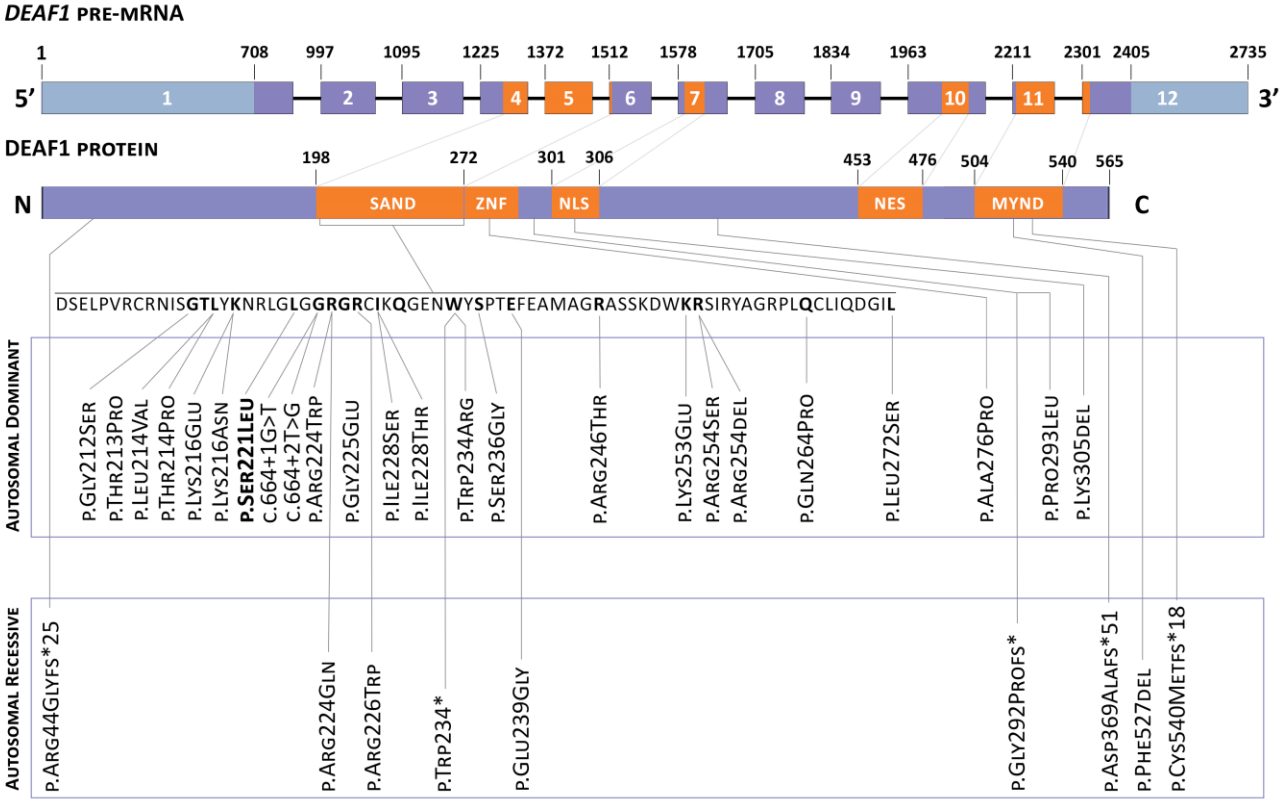

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Figure 1. The structure of the *DEAF1* gene and the spectrum of gene variants detected earlier in patients with VSVS.

In this article we describe a clinical case of a patient who appeared to be a heterozygous carrier of variant c.662C>T in the *DEAF1* gene responsible for the development of the Vulto-van-Sylphout-de-Vries syndrome. The mentioned variant of the *DEAF1* gene was not previously described neither in scientific literature nor in any genomic database.

Autistic behavioral problems together with other signs of patient's phenotype led to performance of a large number of laboratory tests and instrumental investigations during the life of the proband. The results of previous investigations did not reveal a cause of the disease in the patient. Finally, the diagnosis of VSVS was confirmed by whole genome sequencing (WGS) in the patient at the age of 23 when he was hospitalized to a gastroenterological hospital and underwent genetic consultation in the center of personalized medicine.

CLINICAL CASE

A proband is a male patient (Russian/Ukrainian origin) of 23 years old who was hospitalized to the State budgetary healthcare institution "The Loginov Moscow Clinical Scientific Center" of Moscow Healthcare Department with complaints of prominent fatigue, muscle weakness, weight loss, diarrhea (stool up to 2-3 times a day of mushy consistency and small amount, without pathological impurities), and edema of the lower extremities. The patient was accompanied by his mother and could not establish personal or visual contact with the physician upon examination. According to the information obtained from the mother the mentioned complaints of the patient appeared two months ago after taking antibacterial therapy.

Anamnesis vitae: The proband was born at 39 weeks of gestation from the first pregnancy complicated by development of the first trimester toxicosis. Weight and height at birth were 3200g and 53sm, respectively. Early motor development of the patient was normal.

Anamnesis morbi: At the age of 2.5 years old parents noticed that the child showed little interest in social interaction and did not play toys or communicate with other children. Since this age mental developmental regression became evident, phrasal speech was missing, the proband could say only individual sounds and syllables. On the basis of mentioned complaints an autism spectrum disorder (ASD) was diagnosed. Epileptic seizures started at the age of 5 years old. Since then seizures developed every 2-3 months. The proband received symptomatic treatment by anticonvulsants (valproic acid).

Growth retardation in the patient was first noted at the age of 12 years old. Due to abnormal anthropometric characteristics (short stature) of the patient he was observed by an endocrinologist. At the age of 14, due to severe stress and prominent appetite decrease, the patient began to lose weight progressively. At the same time there was also a gradual increase of pain syndrome in the patient because of bloating and rumbling in the abdomen. Chronic abdominal pain lead to sleep disturbance development in the proband. At the age of 16 the boy was hospitalized to the clinic to exclude an endocrine nature of his weight loss and growth retardation (weight 26.5kg, SDS -6.68; hight 143.5sm, -SDS -4.45). According to the X-ray examination (and TW 20) his bone age was 12.7 years old. The diagnosis on discharge was delayed physical and sexual development, cachexia (BMI 12.87 kg/m2, SDS -5.55).

MRI of the brain did not reveal any structural abnormality.

At the age of 22, the patient was first diagnosed with primary hypothyroidism (TSH 11 mIU/ml (0.47-3.41), free T4 0.59 pmol/L (10.2 – 15.5)), and therefore levothyroxine therapy was started. Adrenal as well as somatotropin insufficiency was excluded. An increase of alkaline phosphatase level up to 147 IU/L (30-120), moderate hypoglycemia up to 3.7

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mmol/L (4.9-5.1), an increase of vitamin B12 level up to 2179 pg/ml (189-833) and borderline homocysteine level 12.7 μmol/L (5.5 – 13) were found in the results of biochemical blood tests.

Throughout the patient's life, a large number of different genetic tests were carried out to find out a cause of ASD in the Proband. Numerical and large chromosomal aberrations so as micro deletion and micro duplication syndromes were excluded by karyotyping and DNA-microarray analysis (karyotype 46,XY; molecular karyotype arr(1-22)x2,(X,Y)x1). Molecular analysis of abnormal methylation of the *FMR1* gene promoter region did not reveal any changes typical for Martin-Bell syndrome. Aminoacidopathies and aminoaciduria associated with ASD were also excluded by tandem mass spectrometry of amino acids and organic acids in the blood.

The patient's deterioration that led to the current hospitalization was noted 6 months prior admission to the hospital, after antibiotic therapy of urinary tract infection which was followed by an increase in stool frequency up to 5-6 times a day. An outpatient ultrasound examination of the abdominal cavity, pelvis and retroperitoneal space revealed moderate diffuse changes in the parenchyma of both kidneys of an edematous-infiltrative nature, ascites, diffuse changes of peritoneal layers, and scrotum soft tissues swelling and fluid in the pelvic area. Abdominal X-ray demonstrated intestinal pneumatosis. Abdominal CT showed a small bilateral hydrothorax, pronounced ascites, and an increased amount of gas in the intestinal loops. According to the physician's prescription, the patient was administered metronidazole for 14 days which caused a decrease in stool frequency down to 2-3 times a day. However, due to diarrhea, worsening of the asthenic syndrome and increase of weight loss were reported. A week later, stool frequency rose again up to 6-7 times a day, edema of the lower extremities appeared, weakness increased, and bloating in the abdomen was registered. Upon a consultation with a gastroenterologist of the State budgetary healthcare institution "The Loginov Moscow Clinical Scientific Center" of Moscow Healthcare Department it was decided to hospitalize the patient for further investigation and treatment.

On admission the patient's condition was evaluated as severe. In the somatic status special attention was paid to his short stature (143 cm), signs of hypogonadism and cachexia (weight 31 kg). Neurological status: During the examination the patient was asocial and was generally accompanied by his mother. Consciousness is clear. There were no meningeal symptoms. The patient was sluggish, retarded, demonstrated aggressive behavior and active rejection of examination and medical interventions. It was impossible to establish verbal contact. The patient did not follow commands even to perform simple motor actions. According to the mother, the patient can write, but has not demonstrated any writing skills during the examination. Cranial nerves: sense of smell was not evaluated; fields of vision were not limited; movement of the eyeballs was in full. Convergent strabismus due to the right eye was registered. Medium-sized pupils, S=D. Eye slits were normal, S=D. Direct and cross photoreaction of the pupils were preserved. Convergence was satisfactory. No nystagmus noted. Sensitivity of the face surface was normal. Masticatory muscles strength was 5/5 Medical Research Council Weakness Scale (MRC) points on both sides. The face was symmetrical, mobile. Hearing was not reduced. Swallowing was not impaired. Sternocleidomastoid and trapezius muscles strength was 5/5 MRC points on both sides. The tongue was in the middle line. Muscle tone was slightly reduced. Cachexia. Upper and lower extremities strength was 4/5 MRC points on both sides. Tendon reflexes of medium agility, S=D. No pathological symptoms were noted. The patient was not able to perform coordination tests, but did perform purposeful movements without an action tremor or discoordination. His mother was moving him around in a wheelchair. As part of the hospitalization, the patient underwent routine electroencephalography (EEG), which did not record any typical epileptiform activity.

A gastroenterologist, a nutritionist and a neurologist consulted the patient. Considering that complaints appeared after receiving antibiotic therapy, pseudomembranous colitis was suspected. Differential diagnosis was performed between inflammatory bowel

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disease and celiac disease. CT revealed hydrothorax on the left with the formation of compression atelectasis, signs of gastrostasis, and the picture of inflammatory changes in the walls of the colon, total lesion, active stage, pronounced ascites. According to the laboratory data, there was a decrease in total protein down to 53 g /L (64-83), creatinine to 39 μmol/L (80-115), hemoglobin to 8.2 g/dl (13.0-16.0), an increase in presepsin to 247 pg/ml (0 - 155). Clostridium Difficile was revealed (Toxin A and B positive).

Considering the presence of systemic pathology and ASD signs, consultation of clinical geneticist was performed. The patient's phenotype was characterized by short stature, underweight, impaired posture with kyphosis, superficial location of the saphenous veins and marbling of the skin, multiple diffusely located nevi, freckles and small hyperpigmentation spots on the neck, elongated face, hypertelorism of eyes, short nose, bilateral epicanthic folds, strabismus, opened mouth, dry lips, attached earlobes, impaired dermatoglyphics on the palms (**Fig. 2**).

2A: patient at 5 months of age

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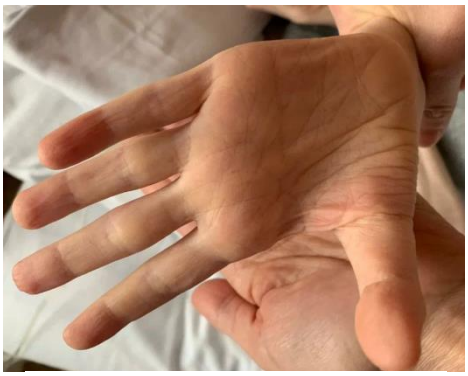
2B: patient at 10 months of age

2C: patient at 4 years old

2D: patient at 6 years old

2E: patient at 23 years old

2B:



2F: dermatoglyphics of palms of the patient at 23 years old

Figure 2. Phenotype of the patient with Vulto-Van Silfhout-De Vries Syndrome at different ages.

No clinical disorders similar to the disease of the proband were revealed in the family history (the patient has a healthy sibling, parents are not relatives to each other) (**Fig. 3).**

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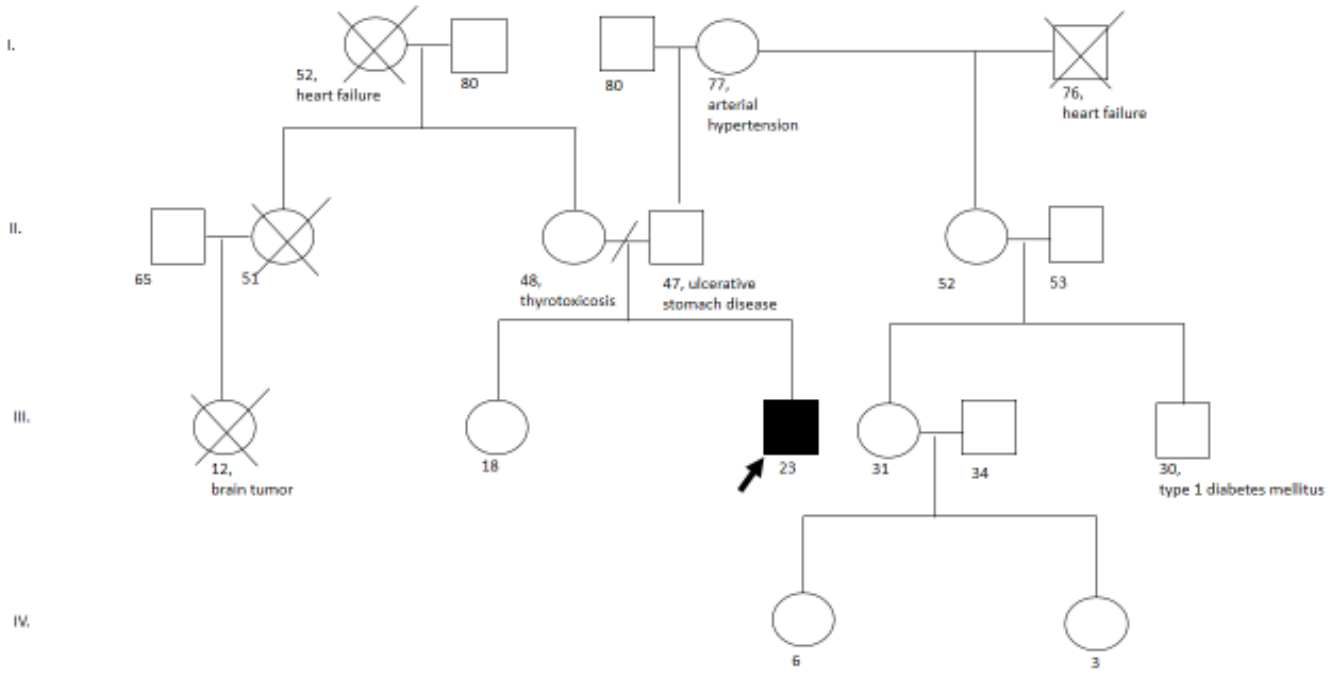

Figure 3. Pedigree of the patient with Vulto-Van Silfhout-De Vries Syndrome.

Taking into account the negative results of the previously performed genetic tests in order to identify a possible genetic cause of the disease the geneticist recommended to perform whole genome sequencing.

According to the results of whole genome sequencing the proband appeared to be a heterozygous carrier of a variant of the nucleotide sequence chr11: 687913G> A (c.662C> T, p.S221L) in exon 4 of the *DEAF1* gene (NM_001293634.1). The identified variant is represented by a missense variant and leads to a substitution of serine for leucine at position 221 of the protein DEAF1. Presence of this variant in the proband was confirmed by automatic Sanger sequencing (Fig. 4A). Subsequently, a segregation analysis was carried out for the identified variant c.662C > T of the *DEAF1* gene in the proband's family using DNA samples from his mother, father, and sister. As a result of Sanger sequencing, the wild type genotype (c.662C/C) was revealed in all relatives studied. (**Figure 4B).**

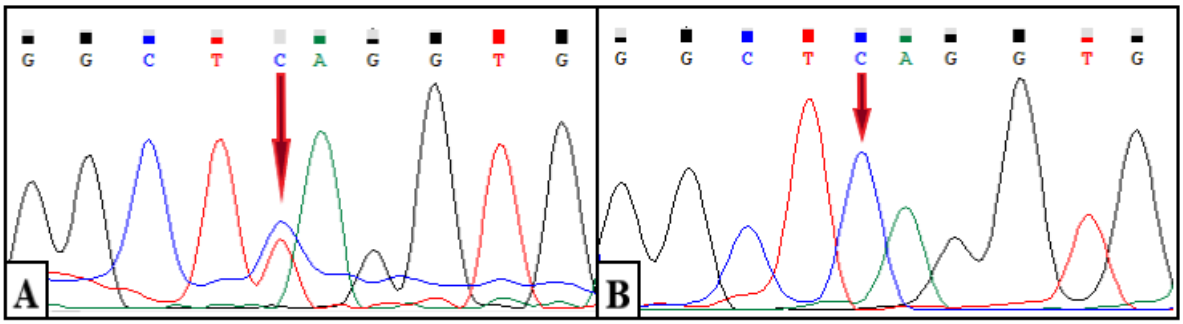

Figure 4. Electrophoregram of the nucleotide sequence of the *DEAF1* gene. **A.** Substitution c.662C> T in the heterozygous state in the proband (indicated by the arrow) **B.** The wild-type genotype at position c.662 in the sister, mother, and father of the proband (indicated by the arrow).

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Referring to international databases to interpret the clinical significance of the identified disorder, it was discovered that this variant had not been previously described in the gnomAD, 1000G, ClinVar, ExAC, Human Genome Mutation and Human Genome Variation. The substitution c.662C_> T is localized in the highly conserved gene region (PM2), the results of ten algorithms for in silico prediction of pathogenicity (BayesDel_addAF, DANN, DEOGEN2, EIGEN, FATHMM-MKL, LIST-S2, M-CAP, MutationAssessor, MutationTaster and SIFT) confirm the pathogenic effect of the variant on the gene, its effect on protein splicing and functionality (PP3), as well as more than 59.4% of variants (including missense mutations) in the SAND domain of the *DEAF1* gene are pathogenic (PM1). This codon previously described the missense variant chr11: 687914A> G (c.661T> C, p.Ser221Pro), annotated as likely pathogenic (PM5). Considering that the phenotype of the proband is highly specific for VSVS (PP4), and as a result of segregation analysis in the family, a "de novo" character of alteration in the patient (PP4) was established, according to the criteria of the American College of Medical Genetics, this nucleotide substitution can be considered as a pathogenic clinically significant variant.

Taking into account the data - complaints, patient medical history and tests performed – the final clinical diagnosis was formulated as follows: VSVS syndrome. Epileptic encephalopathy. Pseudomembranous colitis associated with Cl. Difficile (Toxin A and B positive). Metabolic disorders: hypoproteinemia. Anasarka. Ascites. Cachexia.

Patient treatment included antibacterial and symptomatic therapy to correct water-electrolyte disturbances due to long-term persistent pseudomembranous colitis.

The patient was discharged with some improvement in his condition under the supervision of specialists. Given the history of cachexia, probably within the framework of the identified genetic syndrome, and the associated long-term persistent infection (Cl. Difficile), the prognosis of the patient appears to be poor.

Discussion

ASD is an important medical and social problem to date. It is known that up to 30% of cases of autism are associated with hereditary pathology, both genetic and epigenetic disorders [8]. About 15% of ASD cases occur due to individual «*de novo*» mutations, while variations in the number of copies of chromosomal segment repeats (Copy Number Variation, CNV) additionally cause ASD in 5-10% of patients [9, 10, 11].

To date, 27 patients with VSVS have been reported in the world literature. In 81% of cases (22 out of 27 patients), the diagnosis was made before the age of 19 years old, whereas for the patient described in this article it happened at the age of 23 years old.

All patients had similar clinical manifestations; summarized data are shown in **Tab. 2.** The incidence of symptoms was calculated based on the data analysis from articles available on this issue in the world literature [1,7, 12, 13, 14, 15, 16].

Table 2. The incidence of VSVS syndrome symptoms, according to the data described in the world literature.

Symptom	Incidence according to literature, %	Presence of symptoms in the proband
Delayed psychomotor development	100	+
Gait disturbance	100	+
Autism	87,5	+
Aggressiveness	84,3	+
Hypotension	83,3	-
Dysmorphisms of the face	82,6	+
Poor speech / absence of speech	82,3	+

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Cutaneous syndactyly of the fingers	81,5	-
Epilepsy	79	+
Gastrointestinal abnormalities	75	+
Recurrent infections	72,6	+
Poor eye contact	66,5	+
Sacral fossa	50	-
Converging squint (strabismus)	not described in literature	+
Short stature	not described in literature	+
Cachexia	not described in literature	+

In most of patients, additional nonspecific features have been described, such as hypotension and gait disturbance, high pain threshold, and sleep disturbances [2]

The phenotype of the described patient is very similar to the data presented in the world literature. However, growth retardation and cachexia, not previously described in the articles, are of interest.

Conclusion

ASD is an important medical and social problem and is characterized by impaired neuropsychiatric development of the child with problems of patient interaction with society.

The article describes a patient with ASD and a polymorphic symptom complex, including developmental delay, which was the reason for performing a whole genome sequencing. As a result, a diagnosis of an extremely rare disease called VSVS syndrome was made. The disease turned out to be the result of a spontaneous mutation that occurred in one of the parents' germ cells. The presented clinical case demonstrates the effectiveness of the use of mass parallel sequencing technology to find the cause and establish the prognosis of the disease.

Materials and Methods

All participants signed informed consent prior to genetic testing.

Exome sequencing was performed by next generation sequencing (NGS) on the My Seq sequencing platform (Illumina, the USA), followed by confirmation of the detected genetic variants by Sanger sequencing. Sequencing data results were analyzed using an automated algorithm, including alignment of reads to the reference sequence of the human genome (hg19), post-processing alignment, identification of variants and filtering of variants by sequencing quality, as well as annotation of the identified variants according to all transcripts of each gene from the RefSeq database using a number of predictive programs (SIFT, PolyPhen2-HDIV, PolyPhen2-HVAR, MutationTaster, LRT), as well as methods for calculating the evolutionary conservation of positions (PhyloP, PhastCons).

The recommendations of the American College of Medical Genetics and Genomics (ACMG) were used to annotate the identified variants. Samples from the 1000 Genomes, ESP6500, Exome Aggregation Consortium, and gnomAD projects were used to estimate the population frequencies of the identified variants. The OMIM database, specialized databases about individual diseases, and worldwide literature data were used to assess the clinical relevance of the identified variants.

DNA was isolated from peripheral venous blood samples by the sorbent method (Sample-GS-Genetics, DNA-Technology Research &Production, LLC, the Russia) according to the manufacturer's protocol. DNA concentrations were measured with Qubit 2.0 Fluorometer (Thermo Fisher Scientific) using Qubit™ dsDNA High Sensitivity Assay Kit (Thermo Fisher Scientific). The isolated DNA was then amplified with polymerase chain

reaction (PCR) using oligonucleotide primers. Oligonucleotides were designed using the Oligo software package, according to the main criteria of primers design. To amplify the region of interest in the *DEAF1* gene the following primers were used:

F: 5′- GCCTCTCACCTTCAAACACT-3′;

R: 5′- CCACCACGCTCCACTAATTTT- 3′.

A PCR 25 μl reaction mix contained: 67 mM Tris-HCl (pH=8.8), 1.5-2.5 mM MgCl2, 4 ng of genomic DNA, 5 pM of each primer, 10 mM of dATP, dGTP, dCTP, dTTP and 5 units of active Taq polymerase. Amplification were performed according to the following scheme: 1) denaturation at 95 °C for 5 min; 2) denaturation at 95 °C for 30 sec; primer annealing at 60-64 °C for 30 sec; elongation at 72 °C - 15 sec; 3) final elongation 72 °C - 7 min. Quantitative and qualitative analysis of PCR productivity was performed by electrophoresis in 2% agarose gel. Next, the PCR product was purified on columns. The sequencing reaction was carried out with forward and reverse primers using the BigDyeTM Terminator v3.1 Cycle Sequencing Kit (Applied biosystems by Thermo Fister Scientific, the USA) according to the manufacturer's protocol. Subsequent purification of the sequencing products was performed using the BigDye xTerminator kit (Applied biosystems by Thermo Fister Scientific, the USA). Detection of sequencing products was performed by capillary gel electrophoresis on an 8-capillary 3500 genetic analyzer (Genetic Analyzer 8ch, Applied biosystems by Thermofister Scientific, Hitachi, the USA). Electropherograms were analyzed using the Chromas software package and Sequencing Analysis Software 7 (Technelysium Pty Ltd, Australia).

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Conflicts of interest: The authors declare no conflicts of interest.

Informed consent: Informed consent was signed by patient before the procedure

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