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YETKİN YAŞLI ŞƏXSDƏ 15q11.2 XROMOSOM MİKRODUPLİKASİYASI SİNDROMUNUN DİAQNOSTİKASINA DAİR KLİNİK NÜMUNƏ

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15-ci xromosomun 15q11.2 mikroduplikasiyası ilə əlaqədar törənən genetik sindrom indiyə qədər həkimlərin əksəriyyətinə məlum deyildir. Aparılmış tədqiqatın məqsədi yaşlı şəxsdə bu genetik patologiyanın diaqnostikası üçün alqoritm hazırlamaq və fenotipik cəhətdən bu sindroma bənzər olan genetik xəstəlikdən (Prader-Villi sindromu) diferensiasiyasını araşdırmaq olmuşdur. Məqalədə 15q11.2 xromosom mikroduplikasiyası sindromu olan xəstə haqqında məlumat verilmişdir.

Təsvir edilmiş klinik nümunənin nisbətən yüngülgedişli xəstəliyə aid olması və diaqnostikasının fərqliliyi bu genetik fenomenin əhəmiyyətli dərəcədə variabelliyə malik olduğunu göstərir. Aparılmış müayinələr müşahidə edilən xəstədə təsvir edilən əlamətlərin məhz 15q11.2 xromosom mikroduplikasiyası ilə əlaqədar olduğunu aşkara çıxarmışdır. Bu sindromun diaqnostikasının mübahisə doğurmayan təsdiqinə yalnız molekulyar-genetik tədqiqat zamanı 15q11.2 xromosom lokusunda mikroduplikasiyanın aşkar edilməsi ilə nail olmaq mümkündür.

Açar sözlər: *15q11.2 xromosom mikroduplikasiyası, fenotipik variabellik, molekulyar-genetik tədqiqat*

Ключевые слова: *микродупликация 15q11.2, фенотипическая вариабельность, молекулярно-генетическое исследование*

Key words*: 15q11.2 chromosome microduplication, phenotypic variability, molecular genetic research*

A CLINICAL CASE OF ADULT DIAGNOSIS OF MICRODUPLICATION SYNDROME OF CHROMOSOME 15 AT SITE 15q11.2

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The 15q11.2 microduplication syndrome is a rare genetic disease caused by the duplication of a small segment of the genetic material of the chromosome 15, to date it remains unknown to the physicians.

The aim of the study was to compile an algorithm for diagnosing 15q11.2 microduplication syndrome in adults and differentiating it from a phenotypically similar genetically determined condition (Prader-Willi syndrome). Materials and methods – a clinical case of 15q11.2 microduplication syndrome with mild clinical course was described; neurological, clinical and psychopathological examination was performed, functional diagnostic methods were used.

The described clinical case of a relatively mild clinical course of the 15q11.2 microduplication syndrome and its diagnosis in adulthood indicates a significant phenotypic variability of this phenomenon. This study demonstrates the coincidence of clinical manifestations present in the patient with the currently described symptoms of microduplication of a fragment of the fifteenth chromosome 15q11.2. The results of molecular genetic study with the detection of duplication at the 15q11.2 locus (by STR marker D15S817) are unquestionable confirmations of this syndrome.

Microdeletion and microduplication syndromes are diseases caused by ultramicroscopic deletions or duplications of functionally linked genes on specific regions of chromosomes [1]. Postnatally, a provisional diagnosis is established on the basis of clinical and phenotypic manifestations, and confirmation is based on the results of chromosomal microarray analysis or fluorescent in situ hybridisation [2]. The widespread use of whole-genome analysis,

based on comparative genomic hybridisation, in diagnosis and research has led to an increasing number of microdeletion and microduplication syndromes associated with certain phenotypes [3, 4].

The microdeletion syndrome of the fifteenth chromosome has now been described in more detail [5-8]. The 15q11.2 microduplication syndrome remains unknown to date to the general medical community due to its low prevalence, non-specific phenotype and significant clinical heterogeneity [9, 10]. This pathology, according to studies, is not accompanied by severe malformations of vital organs and does not threaten the life of patients [11]. Studies to date demonstrate the association of *15q11.2* microduplication predominantly with autism spectrum disorders [12], but do not provide a comprehensive description of the patient's neurological and psychiatric status; phenotypic features also remain well-defined at present. The study of patients with *15q11*.2 microduplication syndrome has not been conducted in our country before. This fact determines the relevance, timeliness and prospectivity of this study.

The **aim** of the study was to compile an algorithm for diagnosing *15q11.2* microduplication syndrome in adults and differentiating it from a phenotypically similar genetically determined condition (Prader-Willi syndrome).

Materials and methods of research. The 27-year-old patient was examined after obtaining written voluntary informed consent to participate in the study, with strict adherence to the principles of bioethics as set out in the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and the Universal Declaration on Bioethics and Human Rights (UNESCO); taking into account the principles outlined in the materials for the development of clinical case reporting guidelines [13]. The study was approved by the commission on ethical issues and biomedical ethics of the higher educational institution "Poltava State Medical University" (protocol of the commission meeting № 214 from 23.03.2023).

To describe the clinical case, we used the results of the patient's medical studies, including molecular genetic studies (performed by the Institute of Molecular Biology and Genetics of the National Academy of Sciences of Ukraine) using the next generation sequencing (NGS) technique with the determination of rearrangements at *locus 15q11.2-15q21.1* using STR-markers *D15S817, D15S1513, D15S1002, D15S822, D15S1233* and *D15S659* (the material for the study was venous blood of the proband).

A clinical and anamnestic, clinical and psychopathological examination (using the Stanford-Binet scale [14]), examination by a neurologist and psychiatrist, and a medical geneticist were performed.

Results. We present the description of a clinical case of a patient with microduplication syndrome 15q11.2. 27 years old patient E.R., first applied to the Department of Nervous Diseases with Neurosurgery and Medical Genetics of Poltava State Medical University in 2022.

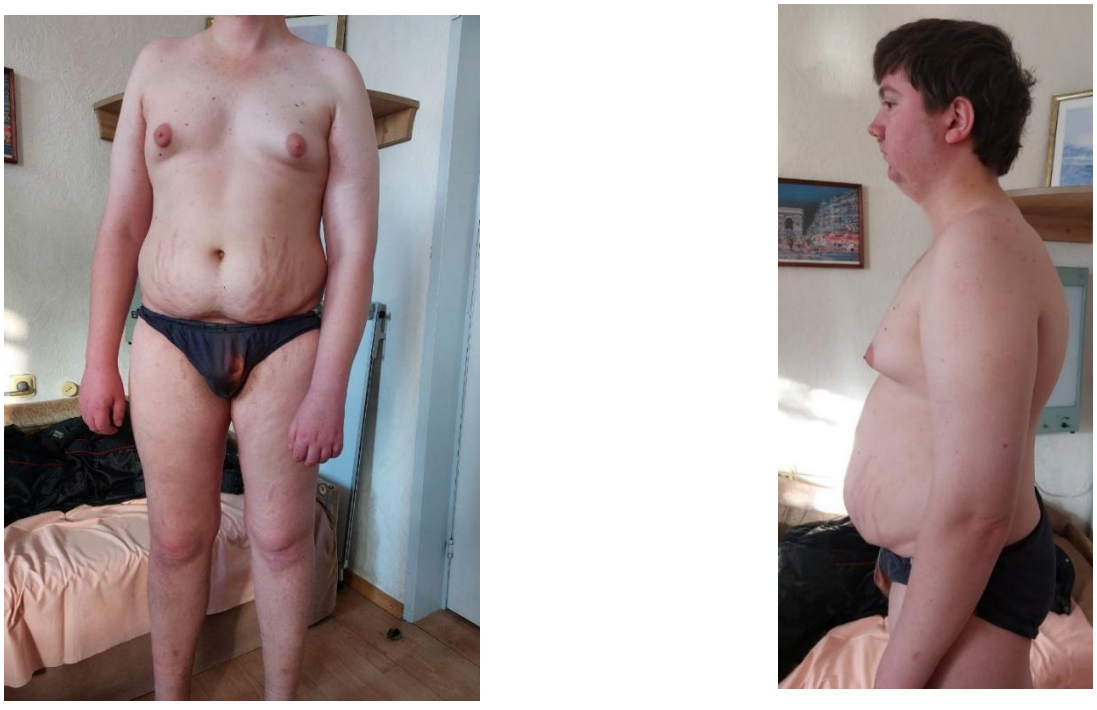
Complaints on examinations were progressive fatigue, lower limb muscle weakness, apathy, insomnia, poor memory, difficulty in expressing own opinion, depression, difficulty in making contact with others, increased appetite, constant feeling of heaviness and intermittent right subcostal pain.

Anamnesis data. Born from the first pregnancy, the first birth. At birth, the mother was 37 years old, the father was 34 years old. The mother reported that the child's father was intoxicated by alcohol during conception. She also admitted the following deviations in her husband: psychological sphere – hypersexuality, tendency to frequent alcohol abuse, suicidal tendencies; phenotypic features – low hairline on the forehead and the back of the head, brachydactyly (short-fingeredness) on the upper and lower limbs. During pregnancy, the motor activity of the fetus was low, the course of labor was without complications. Body weight at birth was 3200 g, height 52 cm. Early neonatal period was without pathology, discharged from the maternity hospital on the 5th day. The child was breastfed until 1.5 years old. Profuse regurgitation was noted during breastfeeding. Since childhood, he has experienced an increased appetite with a tendency to bulimia, oily skin. Prophylactic vaccinations were carried out according to the schedule. Neuropsychological development was delayed (delay in speech development, he started speaking after 3 years old, but the acquisition of speech skills was slow, memorizing words was long-term and difficult); violation of the sleep-wake pattern from early childhood (short-term periods of sleep both at a daytime and at night with longer periods of cheerfulness with

naughtiness, hyperactivity). Since the age of 3 years old, stuttering has been noted. From preschool and early school age, the mother noted in her son lack of attention, poor memory, personal features, namely, stubbornness, low motivation. He suffered from enuresis until he was 14 years old. He graduated from the 9th grade of high school and the vocational-technical lyceum, by profession he is an operator of control and measuring devices, his academic performance was low. Recently, he became prone to alcohol abuse.

Somatic status on examinations were – height 192 cm, weight 125 cm. Body mass index (BMI)=33.91 kg/m2 (corresponding to grade I obesity). Low hairline on the forehead and the back of the head. The face is round, puffy, hyperemic, abundant acne-like rashes, oily skin. General hyperhidrosis, pallor of the skin of the body. Pronounced gynecomastia, fat folds on the chest, abdomen, android type of subcutaneous fat distribution. Numerous striae on the skin of the abdomen, under the armpits, groin areas and the lumbar region (Fig. 1). Sparce hair on the face, absence of hair on the chest. Eyes are of normal size, almond-shaped, flattened bridge of the nose, moderate micrognathia, thin lips, brachydactyly. On the skin of the left upper arm are linear scars from self-cuts. Excessive development of subcutaneous adipose tissue, its distribution is homogenous. Puffiness of the lower legs up to the upper third. The locomotor system has not altered. Breathing is vesicular, no wheezes. The respiratory rate is 18 breaths per minute. Heart sounds are rhythmic, sonorous. The heart rate is of satisfactory properties, 90 bpm. Blood pressure is 130/80 mmHg.

The tongue is rose, coated with a whitish film, moist. There is no hyperemia of the palate. The abdomen is enlarged due to subcutaneous fat, soft, tender palpable in the epigastric area and in the right upper quadrant. The right edge of the liver + 3-4 cm from under the right costal arch. Spleen + 1 cm. Tapping syndrome on both sides is negative. Dysuric phenomena, traces of leakage of urine on the underwear. Feces are well-formed, defecation is daily. Sexual development is delayed (in childhood the proband's mother did not pay attention to this fact, he was not examined by specialists in this regard, the masculinisation index was not determined). At the time of examination, there is hypoplasia of the penis and scrotum, the hair of the external genital area is impoverished. The proband was not examined by an endocrinologist at the examination stage (due to refusal).



A **B**

Fig. 1. The phenotype of the 27-year-old patient Yevhenii R.

The neurological status of the patient is weakness of the abducens nerve on both sides. Deep tendon reflexes on the hands D>S, on the legs D=S. The finger-to-nose test is performed with intentional tremor on both sides. Swaying is observed during Romberg test.

The patient entered the room accompanied by his mother, his movements were calm, his appearance was not neat enough, his clothes were untidy. Confused facial expression. Sociable, comprehensively correctly oriented, answers questions passively, withdrawn, avoids questions related to alcoholism. Consciousness is clear. Attention is increasingly exhausting, insufficient ability to switch. Thinking is slow, consistent, conclusions are logical, but primitive. Accurately makes generalizations and exclusions. No hallucinatory disorders, delusions of perception, or productive thinking disorders at the time of examination were noted. The speech is normal in tempo, moderately pronounced stuttering, the vocabulary is poor, expressions are primitive. The timbre of the voice is high. The patient reports a poor memory. The mood is unstable, hypothymia prevails, prone to irritability. Volitional urges are weakened, hypobolic, passive. Prone to bulimia, alcoholism, low sex drive, does not deny episodic suicidal thoughts, prone to self-harm (self-cutting). Anhedonic. The attitude towards his own condition, social status is indifferent. The ability to communicate is low, autistic, distrustful, has no friends. There are no plans for the future. Not critical of his own condition.

Results of pathopsychological examination: on the Stanford-Binet scale - IQ score of 70 points, which indicates a low level of intelligence, is a borderline indicator with mental retardation. The proband could not cope with traditional methods for determining the level of intelligence in adults (Eysenck, Raven's test), became irritable at the initial questions and refused the test.

Results of the laboratory and instrumental examination. Blood biochemistry test showed bilirubin total 48.1 μmol/L, direct 35.73 μmol/L, indirect 12.37 μmol/L, creatinine 78 mmol/L, urea 4.05 mmol/L, AST 264 U/L, ALT 199 U/L, Seromucoids 6.3 U, Cholesterol 8.4 mmol/L, Total protein 65.4 g/L. Blood glucose 5.5 mmol/L. Insulin 32.4 μIU/ml; the HOMA index is 7.68.

Electrocardiogram: revealed sinus rhythm, HR 76 bpm. Horizontal position of the heart axis. Enlargement of the left atrium. Violation of repolarization processes of a dysmetabolic nature.

Esophagogastroduodenoscopy (EGD) revealed reflux esophagitis A-B, congestive gastropathy. Single erosions of the antrum.

Abdominal ultrasound revealed echo-signs of diffuse changes in the liver with hepatomegaly phenomena without disruption of internal blood flow. Steatohepatosis. Splenomegaly. Diffuse changes of the pancreas. Biliary dyskinesia. Chronic non-calculous cholecystitis, distended gallbladder, gallbladder flexure. Chronic pancreatitis, pancreatic steatosis, salt diathesis.

Brain MRI revealed local leukoaraiosis in the area of the frontal horn of the right lateral ventricle. Hypotrophic changes in the cortex in the area of the frontal lobes of the brain (Fig. 2).

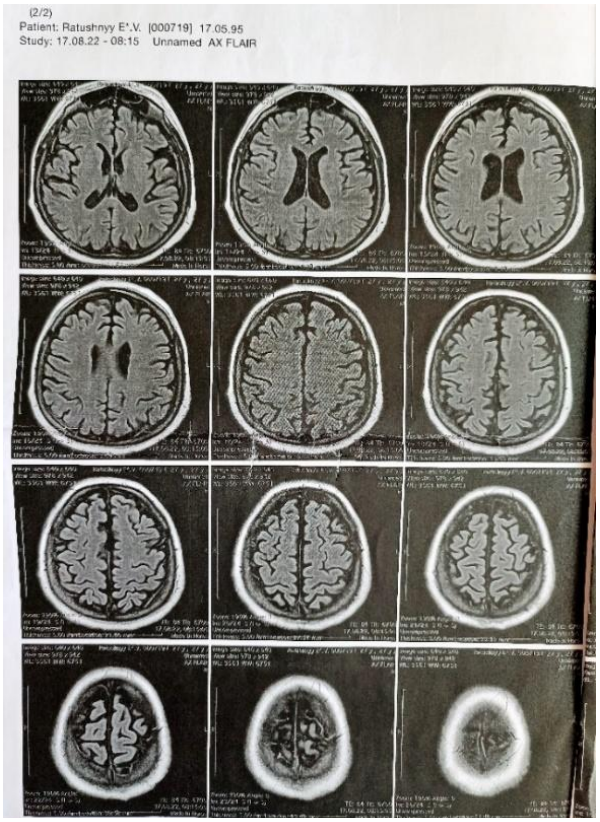


Fig. 2. Brain MRI of the patient with 15q11.2 microduplication syndrome. Local leukoaraiosis in the area of the frontal horn of the right lateral ventricle. Hypotrophic changes in the cortex in the area of the frontal lobes of the brain.

General practitioner has diagnosed chronic hepatitis of mixed genesis, high cytolytic activity, icteric form. Steatohepatosis. Acute cerebrovascular insufficiency of the 1 degree. Chronic cholecystitis. Chronic pancreatitis. Gastroesophageal reflux disease (GERD): with esophagitis, stage A-B (endoscopically).

Neuropathologist admitted residual phenolmena of organic damage to the nervous system with scattered organic symptoms, cerebellar ataxic syndrome.

A preliminary clinical diagnosis was made: Prader-Willi syndrome (phenotypically).

Medical geneticist counselling, molecular genetic analysis was recommended.

The results of the molecular genetic analysis (performed by the Institute of Molecular Biology and Genetics of the National Academy of Sciences of Ukraine): the analysis of rearrangements in the *15q11.2-15q21.1 locus* was performed using the STR-markers *D15S817*, *D15S1513*, *D15S1002*, *D15S822*, D15S1233 and *D15S659*. No deletions/duplication was detected in the *15q12-15q21.1 locus*. A duplication was detected in the *15q11.2 locus* (by the STR-marker *D15S817*).

At the stage of the objective examination, based on a combination of anamnestic information (low fetal movement, tendency to overeat from early childhood, delayed speech development, delay in developing gross and fine motor skills) and phenotypic signs (obesity, almond-shaped eyes, hypogonadism), it was suspected that the patient had a genetic pathology, namely, Prader-Willi syndrome. However, the molecular genetic analysis refuted this diagnosis. The specialists of the Department of Nervous Diseases with Neurosurgery and Medical Genetics had to revise the previously formulated clinical diagnosis in favor of a rare genetic pathology, namely, the *15q11*.2 microduplication, despite the phenotypic similarity of the manifestations to Prader-Willi syndrome.

Discussion. The *15q11.2* microduplication is a rare genetic disease caused by the duplication of a small segment of the genetic material of the chromosome 15. According to the publications [15-18], the presence of additional genetic material on the chromosome 15 affects physical and intellectual development, though phenotypic manifestations can vary significantly, depending on that, for example, which genetic material and how much of it was doubled.

The 11.2 region is located on the long arm (q) near the centromere of the chromosome 15 (marked in pink in Fig. 3) [16].

Despite the different sizes of duplications that occur in this region, they are called microduplications. Previously, duplications were determined by simple band staining (karyotyping). However, most microduplications cannot be detected by this method due to small size. Later, in the 1990s, the FISH (fluorescence *in situ* hybridization) method was developed, which allows for a more detailed study of the chromosome regions. It uses fragments of DNA with a fluorescent label that binds to DNA in specific regions of the chromosome, so this test is only used when there is an assumption in which chromosomal region the change occurs [17].

Currently, more advanced diagnostic methods are available that provide more accurate DNA analysis results, such as microarray comparative genomic hybridization (array CGH) and SNP (single nucleotide polymorphism) microarray analysis [18, 19]. Microarray analysis can detect very small duplications even in cases where phenotypic

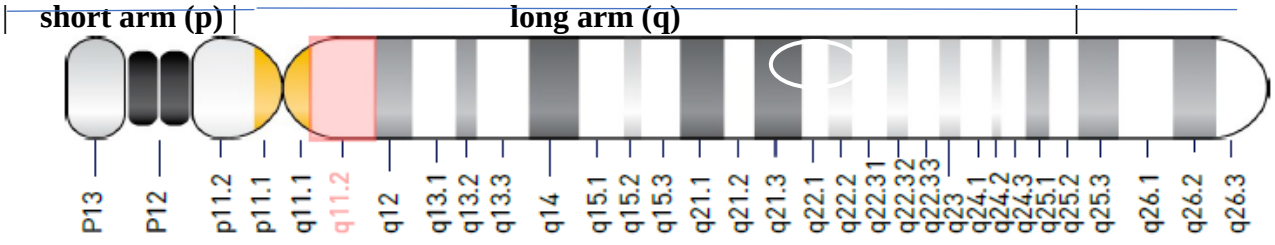


Fig. 3. Chromosome 15

manifestations are absent. It is generally accepted that in the *15q11*.2 microduplication, the duplicated DNA fragment is located next to the initial one, but the matrix analysis does not allow determining the location of the duplicated fragment [20].

Unfortunately, in the reported case, the patient's parents divorced many years ago and lost communication with each other. Both the patient's mother and father categorically refused genetic testing. We were not able to investigate whether the duplication was hereditary, and assigning *de novo* status would also be inappropriate, since the analysis of the parental chromosomes was not performed.

The association of *15q11*.2 duplication with clinical symptoms is still under investigation. Different microduplications can occur at the *15q11*.2 site, some of which are more common than others. They can be mild, asymptomatic, pathogenic, with symptoms, or of uncertain clinical significance [21]. Microduplications most often involve the *15q11*.2 site, also called the Burnside-Butler site [10, 22-24].

Although the symptoms of *15q11*.2 duplications are very diverse, some of the most common are: learning problems, speech disorders, delayed or absent speech development, autism spectrum disorders, behavioural disorders, seizure disorder, impaired sensory processing, anxiety and/or emotional instability, and hypotonia [25]. The results of studies on the Burnside-Butler *15q11*.2 duplication, which is manifested by a tendency to increased appetite and overweight, are also present in our patient, as well as sleep disorders, sleep and wakefulness rhythms. This rare pathology has also been associated with disorders of neatness, grooming, urinary disorders, and significant communication and behavioural problems [15].

Our patient has most symptoms from above list. Among them are delay in language development and its impairment in the form of stuttering, autism and behavioral disorders, disorders in the cognitive and emotional spheres. Notably, the late diagnosis of the *15q11*.2 microduplication syndrome established in our patient can also be explained by the phenomenon of pronounced expressiveness of this mutation.

An innovative feature of this study is the identification of symptoms in the proband we studied that have not yet been described in this genetic pathology (obesity, bulimia, striae, skin greasiness, hypogonadism, depleted hairiness, short-toedness), which initially inclined us to believe that the patient had Prader-Willi syndrome, since some of them are characteristic of this genetic nosology [23, 26].

Facial features characteristic of the *15q11*.2 duplications include a flat back of the head, narrow forehead, flattened bridge of the nose, short nose, upturned nasal tip, low-set ears, long philtrum, micrognathia, thickened lips, high palate. Frequent and profuse regurgitation in the patient in early childhood, reported by the mother, is described in the literature for this pathology, and is most likely associated with micrognathia [27].

The patient's gastrointestinal tract pathology and the phenomena of leukoaraiosis in the area of the frontal horn of the right lateral ventricle, as well as hypotrophic changes in the cortex in the area of the frontal lobes of the brain, have not yet been described in the 15q11.2 duplication syndrome, could be a significant scientific contribution to the clinical description of this genetic pathology. Perhaps they can be a concomitant pathology, or manifestations of a certain type of the 15q11.2 microduplication, which requires additional study.

Thus, if genetic pathology is suspected in a patient referred to a non-specialist (in our case, a neurologist and psychiatrist), it is necessary to proceed sequentially: starting with clinical and anamnestic examination, objective examination of the patient (and his close relatives, if necessary), referral and analysis of laboratory and instrumental methods of research, examination of specialists; but the main point, based on which a clinical diagnosis can be established, are the results of molecular genetic tests.

Conclusions

1. The reported clinical case of a relatively mild clinical course of the *15q11.2* microduplication syndrome and, accordingly, its diagnosis in adulthood, indicates the signi-

ficant phenotypic variability of this phenolmenon. The range of phenotypic manifestations likely depends on the size of the duplication and the duplicated material, as well as the reasons for the origin of the duplication and the unique gene set.

2. The conducted study demonstrates the coincidence of the clinical manifestations present in the patient with the currently described symptoms of microduplication of the fifteenth chromosome fragment *15q11*.2. The next and indisputable confirmation of this syndrome are the results of a molecular genetic analysis with the detection of a duplication in the *15q11.2* locus (by the STR-marker *D15S817*).

3. The question of the complexity of the diagnostic process in medical genetics remains relevant. We made sure of this on our own experience, having passed a long way from being confident in the diagnosis of Prader-Willi syndrome to its refutation, based on the results of a molecular genetic analysis.

4. Conducting a molecular genetic analysis in the clinical work of a medical geneticist is a mandatory and basic stage in the diagnostic and treatment processes. Timely diagnosis and treatment of genetic diseases is crucial in maintaining the quality of life of patients and their families at the appropriate level.

Relationship of the paper with scientific programs, plans and topics. The paper has been written within the scientific research work performed at the Department of Nervous Diseases, entitled "Optimization of the diagnosis, prognosis and prevention of neuropsychological disorders in organic diseases of the nervous system." State registration number 0120U104165.

Financing of the paper. The study has no external sources of funding.

Conflicts of Interest. The authors confirm that the study and the publication of the results were not related to any conflicts regarding commercial or financial relationships, relationships with organizations and/or individuals that could be related to the study, as well as the relationships of the co-authors of the paper.

Ethical Approval. The examination of the patient was carried out upon obtaining the informed consent from him to participate in the study with strict adherence to the ethical principles of medical research involving a person as a research object in accordance with the Declaration of Helsinki.

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КЛИНИЧЕСКИЙ СЛУЧАЙ ДИАГНОСТИРОВАНИЯ СИНДРОМА МИКРОДУПЛИКАЦИИ 15-Й ХРОМОСОМЫ НА УЧАСТКЕ 15q11.2 ВО ВЗРОСЛОМ ВОЗРАСТЕ

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Синдром микродупликации *15q11*.2 – редкое генетическое заболевание, причиной которого является удвоение небольшого сегмента генетического материала 15-й хромосомы, до настоящего времени остается неизвестным для большинства врачей. Проведено исследование с целью составить алгоритм диагностирования синдрома микродупликации *15q11*.2 во взрослом возрасте и его дифференцировки с фенотипически сходным генетически обусловленным состоянием (синдромом

Прадера-Вилли). Продемонстрирован клинический случай синдрома микродупликации *15q11*.2 с мягким клиническим течением; проведено неврологическое, клинико-психопатологическое исследование, использованы функциональные методы диагностики.

Описанный клинический случай сравнительно мягкого клинического течения синдрома микродупликации *15q11*.2 и его диагностирования во взрослом возрасте, свидетельствует о значительной фенотипической вариабельности этого феномена. Проведенное исследование демонстрирует совпадение клинических проявлений, имеющихся у пациента с описанными на сегодня симптомами микродупликации фрагмента пятнадцатой хромосомы *15q11*.2. Неоспоримыми подтверждениями данного синдрома являются результаты молекулярно-генетического исследования с выявлением дупликации в локусе *15q11*.2 (по *STR*-маркеру *D15S817*).

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