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INHERITED 15Q DUPLICATION IN THREE NOT RELATED UKRAINIAN FAMILIES

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Background. 15q duplication syndrome (Dup15q) is caused by the presence of an extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR) within chromosome 15q11.2-q13.1. The syndrome is clinically identifiable and characterized by intellectual disability, hypotonia, motor delays, autism spectrum disorder, epilepsy, and behavioral difficulties [1, 12]. The prevalence of Dup15q in the general population is unknown but may be as high as 1:5000 [10]. The syndrome most commonly occurs in one of two forms: an extra isodicentric 15 chromosome or an interstitial duplication [4]. Most reported cases concern de novo mutation.

Aim. To highlight the importance of genetic testing in patients with neurodevelopmental disorders and emphasizes the need for further research to understand the underlying genetic mechanisms of Dup15q depending on the origin of the inherited duplication.

Materials and methods. The study used next-generation sequencing (NGS), multiplex ligation-dependent probe amplification (MLPA), and karyotype analysis to confirm the interstitial duplication.

Results. We present the phenotype description and diagnostic prospects of three patients from different families who inherited interstitial 15q duplication from a phenotypically healthy mother. The patients exhibited symptoms consistent with Dup15q, including intellectual disability, delayed speech, difficulty understanding spoken language, hyperactivity, epilepsy and sleep disorders.

Conclusion. The inherited interstitial duplication 15q is phenotypical presented only in case of maternal origin and vary in clinical presentation. We suggest as the first choice MLPA method as most cost and time effective in cases of Dup15q suspicion.

Key words: Dup15q, interstitial duplication, maternally inherited, intellectual disability, UBEA3.

Introduction. Dup15q is a clinically identifiable syndrome that results from the duplication (or multiplication) of the 15q11.2-q13.1 region, known as PWACR [12]. Clinical features are characterized by hypotonia and motor delays, intellectual disability, autism spectrum disorder (ASD, in the majority), epilepsy including infantile spasms, behavioral difficulties (hyperactivity, anxiety, or emotional lability) [1] and sudden unexplained death (in the minority). A study using over 30 000 autism clinical cases to search for copy number variants (CNVs) indicates that 15q duplications are the second most common duplication found in ASD, with a frequency approaching 1 in 500 cases [15]. There are also subtle facial differences in people with the syndrome, including an upturned nose, epicanthal folds when the skin fold of the upper eyelid covers the inner corner of the eye, and downslanting palpebral fissures when the opening between the two eyelids slants

downwards [18]. Frohlich et al. have reported the presence of an EEG biomarker involving excessive beta oscillations (12–30 Hz) [5]. The prevalence of dup15q in the general population is unknown but may be as high as 1:5000 [10].

Dup15q syndrome most commonly occurs in one of two forms: an extra isodicentric 15 chromosome (idic15) or an interstitial duplication (int dup15). These clinical findings differ significantly between people with a maternal interstitial duplication and those with a maternal isodicentric supernumerary chromosome [2, 12]. The second ones are typically more severely affected. However, the severity of symptoms varies even among individuals who have increased the dosage by the exact genetic mechanism [2, 9, 12]. The maternal idic(15) variant is reported as de novo in all affected individuals and accounts for ~60-80% of all diagnosed occurrences of the Dup15q syndrome. The remaining 20-40% represent maternal interstitial 15q duplication, out of which the majority of cases (~85%) are still reported as de novo, while the minority (~15%) are maternally inherited [4].

The proximal 15q region includes five regions of segmental duplications or low copy repeats (designated by breakpoints - BPs), which result in increased susceptibility to genomic rearrangements [9]. These five regions are termed BP1 through BP5. The PWACR lies between BP2 and BP3 (~5Mb) and is always included in the interstitial duplications or the idic15 that cause Dup15q. The PWACR is imprinted: maternally derived increases in copy number cause Dup15q syndrome, while paternally derived increases are typically associated with more variable and sometimes different neurodevelopmental phenotypes [3, 18]. This region contains several genes of interest (e.g., ATP10A, CYFIP1, MAGEL2, NECDIN, SNRPN, UBE3A, snoRNAs, and a cluster of genes encoding GABAA receptor subunits). UBE3A is thought to contribute specifically to the intellectual impairment and autism features of Dup15q [6]. UBE3A is imprinted with maternal-specific expression in postnatal neurons and thus expressed at a higher dosage in the brain from individuals with a maternally derived duplication. Paternally inherited 15q11.2-q13.1 duplications do not consistently have an apparent autism phenotype [3, 18]. GABRB3, GABRA5, and GABRG3, genes that encode GABAA receptor subunits, are implicated in the seizures observed in Dup15q [8]. GABRB3 may also contribute to the autism phenotype in Dup15q [2], as single-nucleotide polymorphisms in this gene are associated with autism [13]. HERC2 is an E3 ubiquitin ligase. Individuals with biallelic HERC2 pathogenic variants can have an intellectual disability [17] or a severe Angelman syndrome-like neurodevelopmental disorder [7].

Taking into account the rareness of Dup15q syndrome, we present the phenotype description and diagnosis of three patients from different families who inherited interstitial 15q duplication from a phenotypic healthy mothers.

MATERIALS AND METHODS

Isolation of DNA. For the study, 2 ml of blood was collected from each patient in a tube containing EDTA. Genomic DNA was isolated from peripheral blood by an automated method on a MagCore® PLUS II DNA / RNA Extraction Instrument (RBCBioscience) using the 101 MagCore® Genomic DNA Whole Blood Kit. After extraction, pure DNA with an average concentration of 200 ng/μl was obtained.

Next-generation sequencing (NGS). Genomic DNA obtained from the submitted sample was enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. All targeted regions were sequenced with ≥50x depth. Reads were aligned to a reference sequence (GRCh37).

Multiplex Ligation-dependent Probe Amplification (MLPA). Analysis was performed using the SALSA MLPA Probemix P245 Microdeletion Syndromes-1A kit (MRS Holland, Netherlands) according to the manufacturer's instructions. The mix contains 50 MLPA probes with amplification products from 130 to 499 nucleotides (nt), as well as nine quality control fragments: four DNA quantity fragments (Q-fragments), two DNA denaturation fragments (D-fragments), one control fragment, as well as one X chromosome and one Y chromosome fragment. The disease-targeting probes associated

with the most extensive microdeletions and microduplications next genes: TNFRSF18, TNFRSF4, GNB1, GABRD, REL, PEX13, MBD5, SATB2, DLG1, BDH1, KIAA0226, PIGG, LETM1, WHSC1, CCDC127, PDCD6, TERT, SEMA5A, NSD1, ELN, TRPS1, EXT1, FANCC, PTCH1, GATA3, MKRN3, NDN, SNRPN, UBE3A, SEMA7A. CYP1A1, CREBBP, PAFAH1B1, RAI1, DRC3, LLGL1, NF1, MAPT, KANSL1, IL17RA, BID, CLDN5, GP1BB, SNAP29, PPIL2, RTDR1, ARSA, SHANK3, RABL2B, DMD, MECP2 Exon 1, 3, 4.

For each reaction, 5 μl of DNA with a total concentration of 75 ng was used. Genomic DNA was denatured and hybridized with specific SALSA MLPA probes at 60 °C for 20 h followed by ligation at 54 °C for 15 min. Next, multiplex PCR was performed using single specific primers. All MLPA reactions were performed on a Peqlab peqSTAR 2x thermocycler. Fragment separation and size identification were performed on a SeqStudio (Applied Biosystems) with a 4-capillary system against a GeneScan 600 LIZ size standard. The obtained data were analyzed using software provided by the manufacturer (Coffalyser.net). During the analysis, several reference DNA samples obtained from healthy individuals with a normal diploid copy number were used as controls. Ratios of the number of copies from 0.8 to 1.2 were considered normal.

Karyotype. A cytogenetic study was carried out based on the analysis of cultured lymphocytes of peripheral blood to detect abnormalities in the number and structure of chromosomes. The method of differential staining used was GTG, with the use of trypsin and Giemsa dye (G-bands are dark). The number of segments per haploid set: 500.

RESULTS

Dup15q syndrome was diagnosed in three patients from different families. The first proband is a male who was seen by a geneticist at the age of 4 years due to speech delay, difficulty understanding spoken language, and symptoms consistent with autism spectrum disorder. He was born via cesarean section at 40 weeks following a prolonged labor, weighed 4030 grams, was 56 cm in length, cried immediately after birth, and had Apgar scores of 8/8. His psychomotor development was normal for his age, with head control at three months, sitting at seven months, and walking at 12 months. However, his mother reported that he did not respond to his name, lacked eye contact, and did not seem to understand her from an early age. During the examination, the child exhibited hyperactivity, attention deficit, stereotyped behavior, weak eye contact, echolalia, and large auricles, but had no other congenital malformations. His physical development was normal, but he experienced frequent awakenings at night and had not established neatness skills. He had been working with a team of specialists, including a psychologist, speech and language therapist, and ABA therapist, from an early age, but had not shown improvement in his ability to understand speech, and his stereotyped behavior and vocalizations had increased. He was on a gluten-free and lactose-free diet, and numerous studies were conducted to determine the cause of his symptoms. Cytogenetic analysis revealed a normal karyotype of 46, XY. Metabolic disorders such as amino acid metabolism disorders, organic acidurias, and fatty acid metabolism disorders, as well as Fragile X syndrome, were excluded as possible causes. Biochemical studies indicated that all indicators were within normal ranges, except for the level of serotonin, which was consistently elevated at 592 μg/l compared to the reference range of 50-300. EEG showed no abnormal activity, and MRI of the brain was normal. However, in MRS study of the brain, an increased concentration of alanine, phenylalanine, and glutamine was found. Given the absence of a clear diagnosis, genetic testing was performed using NGS to examine genes involved in the etiology of autism spectrum disorders, which evaluated complete sequencing and deletion/duplication of 2671 genes. The results showed a copy number gain of the genomic region encompassing the full coding sequence of the UBE3A gene. This gain is associated with autosomal dominant dup15q syndrome, and the boundaries of the event extend beyond the assayed region for this gene, potentially encompassing additional genes. Parent-of-origin inheritance

impacts the manifestation of UBE3A-related conditions. MLPA analysis was performed to identify microduplications in the 15q11.2 region in the proband and his mother, and a chromosome imbalance in the form of a duplication of SNRPNU1B, SNRPN-3, and UBE3A-4 genes in the 15q11 region was found in both the proband (Fig. 1) and his mother. Nevertheless, mother – 31 years old women has the same chromosomal imbalance (15q11.2 (P245)x3), she doesn't express any phenotypical abnormalities. Testing of the mother's parents revealed that the region was inherited from her father and caused no symptoms, while the proband's duplication was maternally inherited. The MLPA analysis was performed to mother's 35 years sister and negative result was obtained.

The second proband is a male who was consulted by a geneticist at the age of 9 years due to intellectual disability, epilepsy, severe delay in speech development, stereotypic behavior, and sleep disorders. He was born from the first pregnancy and was delivered physiologically at 39 weeks with a weight of 3900 grams and a length of 55 cm, with 8/8 Apgar points and immediate crying. He did not have any physical or psychomotor development lag - he held his head from 3 months, sat from 7.5 months, and walked independently from 14 months. However, at the time of examination, he did not speak or understand the spoken language and was partially serviced, requiring the help of his mother. Large auricles were observed among the dysmorphias. He has been taking drugs for epileptic seizures since the age of 8. Several genetic studies were conducted, including cytogenetic analysis, which established a normal karyotype (46, XY), also Fragile X syndrome was excluded. Genetic testing was performed on the panel genes involved in the etiology of epilepsy disorders using the NGS method, which evaluated complete sequencing and deletion/duplication of 192 genes. Duplication of the entire coding sequences of UBE3A and GABRB3 genes was found. The parents of the proband were checked, and it was found that his mother carries duplication of the same genes but has no symptoms mentioned before.

The third proband is a male who was referred to a geneticist at the age of 9 years following a neurologist's examination. He was the first child born with a weight of 2950 grams, and presented with stridor after birth, epileptiform activity of focal type, mental retardation, but a phenotype without distinct features. He frequently experiences colds, started walking at 1.5 years of age, and falls often. Genetic testing was performed on the proband using the NGS method to assess a panel of epilepsy genes. This involved complete sequencing and assessment for deletion/duplication of 146 genes. The testing identified a duplication of the entire coding sequences of UBE3A and GABRB3 genes in the proband. Subsequent testing of the proband's mother and maternal grandmother revealed that the mother also carried the same duplication, but it was not maternally inherited, unlike in the proband. In order to visually summarize cases described above, we present Table 2.

DISCUSSION

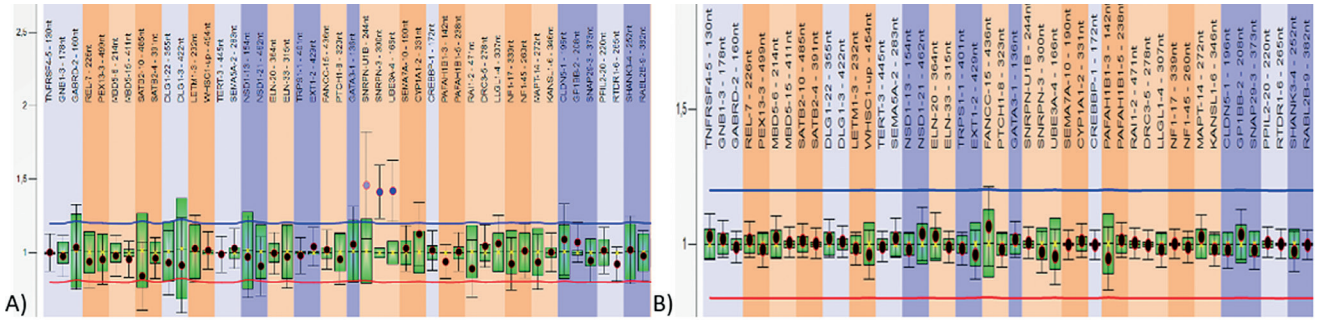

Fig. 1. MLPA P245-A1 analysis of microdeletion syndromes: A – duplication of 15q11.2 involves the following genes SNRPN-U1B, SNRPN-3, UBE3A-4; B – normal profile without imbalance in tested regions.

Table 2

The phenotype description of patient with 15q duplication

Member of	Sex	Age at testing time	15q region's genes (SNRPN-U1B, SNRPN-3, UBE3A-4) copy number	Inheritance	Symptoms
Family 1					
Proband 1	Male	4	copy number = 3	Maternally inherited	Speech and language delay, echolalia, autistic traits, hyperactivity, attention deficit, stereotyped behavior, sleep problems
Mother	Female	31	copy number = 3	Paternally inherited	No symptoms were reported
Aunt	Female	35	copy number = 2	-	-
Maternal Grandmother	Female	60	copy number = 2	-	-
Maternal Grandfather	Male	67	copy number = 3	Unknown	No symptoms were reported
Family 2					
Proband 2	Male	9	copy number = 3	Maternally inherited	Intellectual disability, epilepsy, delay speech development, stereotypic behavior, sleep problems
Mother	Female	38	copy number = 3	Unknown	No symptoms were reported
Father	Male	38	copy number = 2	-	-
Family 3					
Proband 3	Male	9	copy number = 3	Maternally inherited	Stridor, epileptiform activity of focal type, mental retardation, frequent colds, often falls
Mother	Female	36	copy number = 3	Unkown (not maternal)	No symptoms were reported
Maternal grandmother	Female	60	copy number = 2	-	-

The diagnostic process with different molecular-genetic approaches and phenotypical expression of inherited dup15q syndrome in three patients from different families are presented. In the study, three of probands were found to have duplication of several genes (SNRPNU1B, SNRPN-3, UBE3A-4 in the first case; UBE3A and GABRB3 in the second and the third cases). These genes occur in an essential cluster of imprinted genes within the PWACR. When deletions or duplications occur in this locus, a significant susceptibility to develop autism spectrum disorders and skeletomuscular and intellectual developmental impairments is generated [19]. The presence of duplication of previously mentioned genes was identified by MLPA and NGS methods. No abnomalities

were detecterd with standart kariotyping, as the cromosomal changes are below the resolution of these method. The obtained results pointed the importance of additional genetic testing in case of presence of mental retardation with additional phenotypic abnormalities after obtaining normal karyotyping results.

NGS, massively parallel sequencing technology that offers ultra-high throughput, scalability, and speed. The technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA. MLPA alows the studying gene copy number variations (CNVs) in any form, from complete chromosomes to individual exons. Analysis of aCGH also be informative for described cases. We suggest as the first choice MLPA method as most cost and time effective in cases of partial deletion and duplication syndromes suspicion as well for Dup15q.

The boundaries of this event are unknown as they extend beyond the assayed region for this gene and, therefore, may encompass additional genes. All three patients' 15q duplication was maternally inherited as we found the exact extra copies of mentioned genes in their mothers but no duplication in their fathers. Instead of probands, there are no significant deviations in these women. This outcome is caused by different expression of the genes imprinted with maternal-specific mode [3, 18]. We also had a chance to diagnose the maternal grandfather and grandmother of the proband from the first family. As was expected, the grandfather carried the exact duplication (the grandmother did not). Therefore the mother has paternally inherited duplication, which is asymptomatic. The second and third probands, both presenting with epileptic symptoms, were found to have a duplication of the GABRB3 gene. The clinical significance of this variant is currently uncertain as the available evidence is insufficient to determine its role in disease. However, previous research has reported an association between the GABRB3 gene and several conditions, including autosomal dominant developmental and epileptic encephalopathy, commonly known as early infantile epileptic encephalopathy (MedGen UID: 934679), generalized epilepsy with febrile seizures plus, and familial febrile seizures [14]. Once again, it should be noted that the mothers of the probands, who are carriers of the non-maternally inherited duplication, did not report any of the symptoms listed in their own medical histories.

For mothers carrying interstitial duplication 15q, prenatal diagnosis is recommended by employing a sample of chorionic villi or amniocentesis, which can be analyzed by cytogenetic and molecular combination [16]. In maternal interstitial 15q duplication, although penetrance appears to be complete, some individuals may have such mild features as to appear unaffected, reflecting variable expressivity rather than true nonpenetrance [11]. If a mother has the 15q interstitial duplication, the risk to each child of inheriting the duplication is 50%.

CONCLUSION

The inherited interstitial duplication 15q is phenotypical presented only in case of maternal origin and vary in clinical presentation. We suggest as the first choice MLPA method as most cost and time effective in cases of Dup15q suspicion. The obtained data highlights the importance and place of genetic testing methods in patients with neurodevelopmental disorders and emphasizes the need for further research to understand the underlying genetic mechanisms of Dup15q depending on the origin of the inherited duplication.

Conflict of interest. The authors of this manuscript claim that there is no conflict of interest during the research and writing of the manuscript.

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УСПАДКОВАНА ДУПЛІКАЦІЯ 15Q В ТРЬОХ НЕСПОРІДНЕНИХ УКРАЇНСЬКИХ РОДИНАХ

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Актуальність. Синдром дуплікації 15q (Dup15q) спричинений наявністю додаткової материнської копії ділянки критичної для синдрому Прадера-Віллі/Ангельмана (PWACR) у хромосомі 15q11.2-q13.1. Синдром Dup15q клінічно характеризується інтелектуальною недостатністю, гіпотонією, затримкою моторики, розладами аутистичного спектру, епілепсією та поведінковими розладами [1, 12]. Поширеність Dup15q у загальній популяції невідома, але може сягати 1:5000 [10]. Цей синдром може бути результатом однієї із двох перебудов: додаткова ізодицентрична 15 хромосома або інтерстиціальна дуплікація [4]. Більшість зареєстрованих випадків стосується мутації de novo.

Ціль: Визначити походження перебудови та описати фенотип у пацієнтів із рідкісним синдром Dup15q.

Матеріали та методи. У дослідженні використовували мультиплексну лігазно-залежну ампліфікацію зонда (MLPA), результати секвенування наступного покоління (NGS), і аналіз каріотипу для підтвердження інтерстиціальної дуплікації.

Результати. Ми представляємо опис фенотипу та діагностичний процес у трьох пацієнтів із неспоріднених родин, які успадкували інтерстиціальну дуплікацію 15q від фенотипово здорової матері. Пацієнти демонстрували симптоми, що відповідають Dup15q, включаючи інтелектуальну недостатність, затримку мовлення, труднощі з розумінням усної мови, гіперактивність, епілепсію та розлади сну.

Висновки. Успадкована інтерстиціальна дуплікація 15q проявляється фенотипово лише у випадку материнського походження і варіюється за клінічними проявами. Ми пропонуємо використовувати метод MLPA першочергово, оскільки він є найбільш доступний по вартості та часу у випадку підозрювання синдрому Dup15q.

Ключові слова: Dup15q, інтерстиціальна дуплікація, успадкування по материнській лінії, порушення розумового розвитку, UBEA3.