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The first case of two rare lysosomal storage diseases in identical twins

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For the first time in the medical literature, a combination of two rare lysosomal storage diseases — mucopolysaccharidosis type IVA (Morquio disease) and Krabbe disease — was identified and genetically studied in identical twins. For genetic diagnostics, the Next Generation Sequencing modern technique was used. It was used as a new molecular-genetic diagnostics technique with vast diagnostic opportunities. The diagnostics panel consisted of primers corresponding with 14 lysosomal storage diseases. Two different mutations of N-acetylgalactosamine 6-sulfatase gene: ENSG00000141012/ NM_001323543 c.463G>T (p.Gly155Cys) and N-acetylgalactosamine 6-sulfatase: ENSG00000141012/ ENST0000026869 c.1018G>T (p.Gly340Cys) were found in double heterozygous state. N-acetylgalactosamine 6-sulfatase gene mutation c.1018 G>T (p.Gly340Cys) was first identified in a patient from Azerbaijan. Both mutations of N-acetylgalactosamine 6-sulfatase gene were classified as pathogenic and related to class 1, corresponding with Recommendations of Centogene® and ACMG®. For the first time, patients of Azerbaijani origin were identified and genetically studied for Krabbe disease, and a novel mutation - c.1834+5_1834+9delinsGTGACT was detected in a homozygous state. Genetic analysis of their parents showed their heterozygous mutation state and confirmed galactosylceramidase gene's homozygosity.

Keywords: *Mucopolysaccharidosis IV type, Morquio disease, Krabbe disease, Next Generation Sequencing technique*

INTRODUCTION

Mucopolysaccharidoses (MPS) is a group of inherited metabolism diseases linked to metabolic disturbance of glycosaminoglycans leading to organs and tissues being affected. These diseases are conditioned with gene mutations that instruct the macromolecule intra-lysosomal hydrolyze process. Mucopolysaccharidosis IV type (MPS IV) has the name of Morquio Syndrome - (synonyms: Morquio disease, spondyloepiphyseal dysplasia, chondroosteodystrophy, deforming osteochondrodystrophy, Morquio - Brailsford syndrome, Morquio - Ulrich syndrome). Morquio Syndrome was described first in 1929 by Uruguayan doctor Louis Morquio (1888-1935) and James Frederic Brailsford (1888-1961), a British roentgenologist in Birmingham, England. Clinic manifestations are characterized by significant skeletal deformations, especially in the chest. Differing from other MPS types, MPS IV type is specified by the absence of retardation, corneal opacity, hepatosplenomegaly, and grotesque face features (Borlot et al., 2014; Brailsford et al. 1929).

The disease is modified by deficiency of two lysosomal hydrolases located in two different genes GALNS (galactosamine N-acetyl-6-sulfatase) and GLB1 (galactosidase beta 1). A

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deficiency of galactosamine N-acetyl-6-sulfate sulfatase enzyme was observed with MPS IVA, whereas MPS IVB had a β-galactosidase enzyme deficit. The GALNS gene (MPS IVA) is in the chromosome 16q24.3 site. In MPS, the IVB GBS gene is in the 3q21.33 site. It is important to notice that β-galactosidase encoding gene mutation leads also to gangliosidosis Type 1. The inheritance type of this disease is autosome-recessive. Prevalence of MPS IVA is 1:250 000 newborns, MPS IVB is encountered rarer (Caciotti et al., 2015; Charrow et al., 2015).

There are different clinic forms of MPS IV type: severe or classic, intermediate, and light. The disease is determined with keratan sulfate storage in connective tissue and is characterized by significant skeletal deformation and growth retard. All the above enumerated signs lead to disabilities, and in severe disease course - to lethality (Charrow et al., 2015, Tomatsu et al., 2015). The average frequency of MPS IV type (Morquio syndrome) among live newborns throughout the world equals 1:420000.

It should be noted that population genetic studies have investigated the biochemical characteristics and genetic heterogeneity of Morquio disease in various regions of the Republic of Azerbaijan (Alizada et al., 2022; Alizada et al., 2022).

Krabbe disease (glucosylceramide lipidosis) is a rare lysosomal storage disease. The disease is caused by enzyme deficiency of cerebroside galactosidase encoding galactosyl ceramidase gene (GALC) in deficiency of which galactosyl ceramide and galactosphyngosine are being stockpiled. It is inherited autosome recessive. The disease was named after Danish neurologist Knud Haraldsen Krabbe, who described it in 1916 (Giri et al., 2006; Shin et al., 2016; Spratley et al., 2016).

The clinical picture is one of the severest rare encountered genetic pathologies (synonyms could be globoid cell leukodystrophy or glucosylceramide lipidosis). This disease was seen for the first time ever by pediatricians, family doctors and neuropathologists. Kids were usually born with normal appearance, and at 2-3-month age muscle tonus was increased (spastic type), hyperexcitability for sound, light, tactility, crying without any reason, nonmotivated temperature rise, difficulty when breastfeeding. Often at the first stage of the disease course those symptoms could be accepted as traits of infantile cerebral paralysis. It is a complicated disease that progresses very quickly and leads to lethality. Cerebroside β-galactosidase enzyme necessary for lipid breakdown is not functioning properly in Krabbe disease. Those lipids stockpile and affect nerve-wrapping tissue (myelin sheath) formation (Spratley et al., 2016).

The highest prevalence of Krabbe disease has been reported among Palestinians, with an incidence of approximately 1 in 6,000 live births. In the USA it was 1:100000, in Scandinavian countries - 2:100000 live newborns (Shin et al., 2016). It should be noted that the clinical manifestation of Krabbe disease in the Azerbaijani population is not yet described.

Considering the presence of complicated and unclear clinical manifestations resembling lysosomal storage disease in identical twins, the goal of the research was to identify disease diagnosis with genetic studies by means of diagnostics modern molecular genetic methods and techniques.

MATERIALS AND METHODS

The study materials were 9-month-old girls-identical twins. The parents were not relatives. Mother of girls originated from the Guba region located in the northern-east part of the Azerbaijan Republic. Father was from the Zagatala region located in the northern-west part of the Republic. At the time of the girls' birth, mother was 21 years old, and father - 25. Twins were born on time with a 9 score on the Apgar scale with normal weight and height.

Genetic studies used venous blood of 2 ml with heparin as an anticoagulant. Prior to sampling, written consent was obtained from parents.

To confirm suspicious clinical manifestations, genetic analysis at the DNA level was performed. Genetic study was carried out with NGS (Next Generation Sequencing) technique. To isolate DNA, a QIAamp DNA Blood mini kit (Germany manufactured) was used. Analysis was carried out on the panel-

designed MiSeq Illumina apparatus manufactured by Illumina® (USA). The panel included the following genes: GALNS, IDUA, GALC, SUMF1, GAA, GUSB, GBA, GLB1, ARSB, PAH, SMPD1, ADGRV1, and PLA2G6. Sequencing of the GALNS gene at the DNA level was performed with the NGS technique (Next Generation Sequencing). There were used the following kits and programmes: kit - Lysosomal Storage Disease Kit, Celemics®; Analysis Platform - MiSeq Sequencing, Illumina®; Analysis programme - SEQ analysis platform, GENOMIZE® (http://seq.genomize.com), GRCh37(h19).

"DNA samples with their gene mutations were identified on that panel with the Next Generation Sequencing technique. More than 99% of gene coding sites were studied with a reading depth of not less than 50X. The mean reading depth was 1559 indications. The analysis included exon-intron linkage (±10 n.p.)." The pathogeny classification of the obtained results was conducted correspondently to "Guidelines of ACMG®".

RESULTS AND DISCUSSION

From 2018 to 2023, extensive work was carried out in the Republic of Azerbaijan to identify and study the genetics of lysosomal storage diseases in patients with a genetic predisposition. Populational medical genetic studies were conducted in patients in Baku city, Gyandzha as well as among children of Kyurdamir, Sabirabad, Shirvan, Guba, Khachmaz, Lankaran and Astara economic administrative areas of the Republic. Patient examination in those areas was managed in the Central clinics in the presence of doctor-pediatrician and doctor-geneticist.

The epidemiological studies carried out in many administrative regions of the Republic allowed us to identify and study genetically five types of MPS diseases. They are as follows: MPSI (Hurler), MPSII (Hunter), MPSIII (Sanfilippo), MPSIV (Morquio), MPSVI (Maroto-Lami). There are 34 affected people altogether. Two identical twins had clinical manifestations of Morquio syndrome (MPSIV). The patients exhibited coarse facial features, rough skin, a short thorax, chest deformities, and X-shaped leg deformities. In addition, the female patients showed neurological disorders not typically associated with Morquio syndrome, such as sleep disturbances, seizures, and epileptic episodes. Both physical and mental developmental delays were present. Thus, the clinical presentation in these twins was notably complex. Genetic diagnostics were performed using the NGS technique with a panel targeting mutations in 13 genes associated with lysosomal storage diseases.

At the Republic Central Children's Clinical Hospital in Baku, two girls, identical twins, were identified with a complex clinical presentation resembling multiple lysosomal storage diseases. Their parents and siblings were also examined.

Clinical examination was carried out by a pediatrician and a geneticist. Due to the unclear and complex clinical manifestations observed in the twins, the specialists decided to conduct a more comprehensive genetic study. They opted to use modern genetic analysis based on the Next Generation Sequencing (NGS) technique. To design the diagnostic panel, primers targeting several diseases with similar phenotypic traits, particularly lysosomal storage disorders, were included.

Blood samples were taken to the GENOM clinic laboratory in Baku city for further genetic analyses.

The diagnostic panel consisted of primers for 14 lysosomal storage diseases; they were as follows: Krabbe disease (GALC gene), mucopolysaccharidosis type II - Hunter disease (IDS gene), mucopolysaccharidosis type IVA (GALNS gene), mucopolysaccharidosis type IVB (GLB1 gene), mucopolysaccharidosis type VI (ARSB gene), Fabry disease (GLA gene), multiple sulfatase deficiency (SUMF1 gene), Gaucher disease (GBA gene), gangliosidase (GM1 gene), gangliosidosis - (GLB1), mucopolysaccharidosis type I (Hurler Disease) (IDUA gene), mucopolysaccharidosis type VII (Leya disease) (GUSB gene), juvenile Parkinson disease (CAA gene), Niemann-Pick disease (SMPD1 gene).

Genetic testing revealed mutations in two genes, GALNS and GALC, which are associated with MPS IVA (Morquio disease) and Krabbe

disease, respectively. The results of the genetic analysis of the identical twins are presented in Table 1. Table 1 shows a fragment of NGS analysis pointing out two GALNS gene mutations and one GALC gene mutation. Here were applied the followings: the Software Version:6.14.0| VariantCall Version:15.4.3| Annotation Version: Print Date: 23 January 2022 information about variants from SEQ account; Analysis Parameters were: Primary Coverage Threshold (alternative allele)=5; Secondary Coverage Threshold (alternative allele)=50; Strand Bias Metric Threshold (SBM) for Heterozygote Calls =8.0; Alternate Allele Ratio Threshold For Heterozygote Calls=0.0; Minimum Alternate Fraction For Variant Calling =20.0; Read End Masking=0; Mismatch Read Filter=0; Require Allele Ratio Evidence From Both Strands =False.

Table 1. GALNS and GALC gene mutations identified in identical twins.

Gene/mutation	Zygosity	ACMG classification	Disease name and type
GALNS:ENSG00000141012/NM_001323543 c.463G>T (p.Gly155Cys)	Heterozygote	VUS*	Mucopolysaccharidosis IVA
GALNS:ENSG00000141012/ENST0000026869 c.1018G>T (p.Gly340Cys)	Heterozygote	VUS*	Mucopolysaccharidosis IVA
GALC:ENSG00000054983/ENST00000261304 GTCAG>AGTCAC c.1834+5_1834+9delinsGTGACT)	Homozygote	VUS*	Krabbe disease

*VUS - unclear mutation of clinical significance

The table presented the nomenclature number and mutation type, zygosity, classification according to ACMG®, name and disease type.

The GALNS gene in those siblings had two different missense mutations in the heterozygous state. Consequently, patients had double heterozygosity - differing mutations of one the same GALNS gene (compound state).

The first mutation consisted of the substitution of nucleotide Guanine with nucleotide Thymine in position 1018 in the GALNS gene (c.463G>T/ c.1018G>T).

In the presence of c.463G>T substitution of Glutamine amino acid with Cysteine amino acid took place in position 155 in the composition of newly synthesized protein (p.Gly155Cys). Mutation c.1018 G>T led also to the substitution of Glutamine amino acid with Cysteine amino acid in position 340 of the synthesized protein (p.Gly340Cys). GALNS gene c.1018 G>T (p.Gly340Cys) mutation in the heterozygous state was identified for the first time in the Azerbaijani population. Both mutations were classified as pathogenic and related to pathogenic class 1, in accordance with "Recommendations of Centogene® and ACMG®". Genetic analysis of the GALNS gene in siblings' parents showed heterozygous state c.463G>T for their father and c.1018G>T mutation for their mother. Our results in these studies haven't been ever registered and published in scientific papers and references.

Patients had the following GALC gene mutation c.1834+5_1834+9delinsGTGACT in the homozygous state. GALC gene genetic analysis for both parents revealed the heterozygous state of the said mutation. There are no references in world medical literature for this mutation. Consequently, this is a novel mutation and identified by us for the first time.

The GALC gene is located in Chromosome 14 (14q31) and has seventeen exons 156k nucleotide pares long. Normally GALC gene mRNA is most intensively expressed in nervous and kidney tissues. Galactocerebrosidase protein encoded with this gene consists of 685 amino acid residues and weighs around 77kDa. In mutation, the deficiency of galactoceramidase enzyme merges. That enzyme breaks down galactocerbroside, the simplest of glycolipids, into galactose and ceramide. Galactocerbroside is the most key component of myelin that forms a defending cover around nervous fibers providing speedy nervous impulse transfer. According to medical references, Krabbe disease occurred in 1:100 000 live newborns. More frequently the disease was encountered in the

Scandinavian peninsular population - 1:50 000 as well as in Israeli Arabs (Palestinians) 1:6000. In 85% of all cases, Krabbe disease was identified in children born from consanguineous marriages. Sometimes parents could be carriers of the defect gene, but they had no affect manifestations. In that case, they had a 50% reasonable probability of childbirth with leukodystrophy (Shin et al., 2016).

The ClinVar database lists 294 mutations in the GALC gene, of which 41 are classified as pathogenic. Approximately half of these are single nucleotide substitutions, while the second most frequent type consists of duplications. About 25% of the pathogenic mutations are deletions and insertions. According to the OMIM database, ten of these mutations are considered the most clinically significant. Pathogenic mutations have been reported across all 17 exons of the GALC gene (Brailsford et al., 1929). The onset and severity of Krabbe disease may vary even among members of the same family. The mechanisms underlying such variability are not yet fully understood. However, in patients with late-onset Krabbe disease, the most frequently observed mutation is p.Gly41Ser (Giri et al., 2006; Spratley et al., 2016).

The genetic study of Krabbe disease in the identical twins was the first of its kind conducted in our Republic. This was largely due to insufficient awareness among physicians regarding these rare diseases, as well as the inherent diagnostic challenges they present.

During the screening of genetically burdened children for various types of mucopolysaccharidosis (MPS), 56 patients were identified as suspected cases. Among them, 32 were diagnosed with Morquio disease (MPS IVA and MPS IVB) in either homozygous or heterozygous states (Alizada et al., 2022).

It should be mentioned that earlier conducted epidemiological studies of lysosomal storage diseases in various areas of the Azerbaijan Republic revealed a lot of GALNS gene mutations. It should be noticed, that ENSG00000141012/ ENST00000268695 c.1018G>T (p.Gly340Cys) mutation was identified for the first time among all GALNS variants found previously.

The next Table 3 presents the genetic study results for GALNS and GLB1 genes of thirty-two patients revealed with MPS IV diagnosis. It showed MPS type, Gene name, Variant Coordinates, Amino acid change, Type and Classification change.

Enzyme with the following genetic analysis of the GALNS gene identified five mutations: c.157G>A, c.439T>A, c.443A>G, c.553C>T, c.1283A>G, c 1144C>G, c.1265A-G, c. 463G-T; c.1018 G-T specific for MPS IVA and one mutation c.1448T>C in GLB1 specific for MPS IVB. All nine GALNS mutations are missense mutations.

Seventeen (50.0%) out of 34 patients with MPS were diagnosed with Morquio syndrome. The majority of these patients (94.12%) had Morquio A type, while only 5.88% had Morquio B type. The ratio of Morquio A to Morquio B was 16:1, compared to a 6:1 ratio reported in other populations.

In population-based studies conducted in the Republic, 20% of the 34 patients with MPS were diagnosed with Sanfilippo syndrome (types A, B, and C), 14.7% with Hunter syndrome, 5.9% with Hurler syndrome, and 7.7% with Maroteaux–Lamy syndrome.

Our analysis of epidemiological study references on MPS conducted in world human populations in all six continents showed the following frequency type distributions. In contrast to the Azerbaijan Republic population, they had the highest frequencies for Sanfilippo syndrome - 28.7%, the lowest for Maroto-Lami -7.4%. Hunter and Hurler syndromes had the same frequencies – 20%. Morquio A and B, both types together, were on the 4th line and equaled 18.03%. The average frequency of Morquio syndrome for world continents' populations distributed as follows: Australia -8.8%, Asia -17.6%, America-19.9%, Africa -21.0% and Europe -22.9%. The highest frequency in Europe was observed for Ireland population -32.0%, in Asia it was Israel -31.2%, in Africa Saudi Arabia showed 29.6%, and in South America Columbia had the highest frequency -60.0%. Azerbaijan was right after Columbia, and that MPS type gave 50.0% of all MPS types identified till now. As to MPS mutation types identified, the majority of them in our studies were missense mutations. Small deletions and splice site mutations were little

observed.

Identified mutations were in homozygous, double heterozygous and heterozygous states. The majority of patients had homozygosity on one mutation. Hence, the parents of the patients had consanguinity. All identified mutations related to missense mutations, and in accordance with "Recommendations of Centogene® and ACMG®", those mutations were classified as pathogenic of class 1.

Adding earlier found GALNS gene mutation c.1018G>T (p.Gly340Cys), altogether up to now there are seven different mutations leading to Morquio disease (MPS IV) in the Azerbaijani population. All those seven mutations are missense mutations. However medical literature analysis shows different mutation types of GALNS and GLB1 genes as small and big deletions, translocations and transversions. At the same time, we should notice, that frequency of MPS IVA is higher than MPS IVB at a ratio of 6/1, which corresponds with literature data (Alizada et al., 2022; Alizada et al., 2022; Chuang et al., 2021; Khan et al., 2017; Latifa Chkioua 2015; Nelson et al., 2003).

Table 2. Identified GALNS and GLB1 mutations

MPS IV Gene	Variant coordinates	Amino acid change	Type and classification
MPS IVA, GALNS	NM_001323544.1:c.157G>A	p. Gly 53Arg	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1:c.439T>A	p. Trp147Arg	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1:c.443A>G	p. His148Arg	Missense Pathogenic (class 1)
MPS IVB, GLB1	NM_000157.3: c.1448T>C	p. Leu483Pro	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1: c.553C>T	p. Pro185Ser	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1: c.1283A>G	p. Gln428Arg	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1:c 1144C>G,	p. Leu382Val	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1: c.1265A-G	p. Gln422Arg	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1:c. 463G-T;	p. Gly155Cys	Missense Pathogenic (class 1)
MPS IVA, GALNS	NM_001323544.1:c.1018 G-T;	p. Gly340Cys	Missense Pathogenic (class 1)

A family with two kids – identical twins diagnosed with two rare lysosomal storage diseases: Morquio syndrome and Krabbe disease. In the world, the frequency of Morquio syndrome was registered as 1:420000 live-born newborns whereas Krabbe disease frequency was known as 1:100000 live newborns. In the family with non-consanguineous parents, we identified a combination of these two rare syndromes. That fact speaks for high frequencies of mutated GALNS and GALC genes in the Azerbaijani population.

The practical conclusion of our studies highlights the importance of educational efforts both among the general population and healthcare professionals. Timely identification of affected children can assist physicians in adjusting treatment strategies appropriately. The identification of families at genetic risk, those with children diagnosed with Morquio disease, enabled us to perform prenatal diagnostics on three fetuses in subsequent pregnancies. In all three cases, the children were born clinically healthy and carried a heterozygous genotype: two with the c.439T>A/N variant and one with the c.443A>N variant (Alizada et al., 2022).

Considering the high frequencies of MPS in the population of the Azerbaijan Republic, we plan to propose fetus prenatal diagnostics to families with the genetic burden of the disease with the purpose of prophylaxis.

CONCLUSIONS

- For the first time in global medical literature, a combination of two rare lysosomal storage diseases—Morquio disease (MPS IVA) and Krabbe disease—was identified and genetically studied in a pair of identical twins by our research group
- Morquio disease presented by two different GALNS gene mutations

GALNS:ENSG00000141012/NM_001323543 c.463G>T (p.Gly155Cys) and GALNS:ENSG00000141012/ENST0000026869 c.1018G>T (p.Gly340Cys) in double heterozygous state.

- GALNS gene mutation - c.1018G>T (p.Gly340Cys) - was identified for the first time in patients-girls in Azerbaijan.
- Both GALNS gene mutations were classified as pathogenic and related to class 1 in accordance with "Recommendations of Centogene® and ACMG®"
- For the first time patients of Azerbaijani nationality were identified by scientists, and studied the genetics of Krabbe disease, whereas c.1834+5_1834+9delinsGTGACT a new mutation of GALC gene was found in the homozygous state.
- Considering the reproductive age and the parents' desire to have healthy children, we plan to perform prenatal diagnostics in future pregnancies.

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