

Molecular study of IDUA, IDS, GALNS and GLB1 gene mutations in the Azerbaijan population

Sevda Alizada¹, Shir Khan Musayev², Elkhan Rasulov²

¹Azerbaijan Medical University, 167 Samad Vurgun Str., AZ1022, Baku, Azerbaijan

²GENOM Clinic Laboratory, White City, 3 Central Bulivard, AZ1025, Baku, Azerbaijan

For correspondence: alizadasevda@yahoo.com; lab@genom.az; dr.rasulovelkhan@gmail.com

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For the first time in the Azerbaijan Republic, we carried out medical genetic consultation of affected children suspicious of lysosomal storage diseases, and particularly with mucopolysaccharidoses. Patients were from the cities of Baku, Gyandzhe and other areas of the Republic. Consultations were done by doctors: pediatrician and geneticist. As to clinical manifestations, 19 index patients and 54 members in their families: Hurler syndrome (1 patient), Hunter syndrome (5 patients), Morquio syndrome (13 patients). The NGS (Next Generation Sequencing) technique was used for molecular genetic diagnostics. In index patient suspicious with Hurler syndrome (MPSI) mutation of alpha-L-iduronidase (IDUA) (NP_000194.2: c.1882C>T, p.Arg628Ter) was identified in the homozygous state. Among patients with clinical manifestations of Hunter syndrome (MPSII) three mutations iduronate-2-sulfatase (IDS) gene: 1106C>G (p.Asp358Leu), c.322T>G (p.Asp358Leu) and c.1215del (p.Leu*34406Phefs) were identified in the hemizygous state. In patients with Morquio syndrome (MPSIVA) 9 mutations of the N-acetylgalactosamine-6-sulfatase (GALBS) gene and one mutation beta-galactosidase (GLB1) c.176G>A (p.Arg59His) Morquio syndrome (MPSIVB) were identified. Nine mutations are as follows: c.1144C>G (p.Leu382Val), c.1265A>G (p.Gln422Arg), c.463G>T (p.Gly155Cys), c.1018 G>T (p.Gly340Cys), c.157G>A (p.Gly53Arg), c.553C>T (p.Pro185Ser), c.443A>G (p.His148Arg), c.1283A>G (p.Gln428Arg), c.439T>A (p.Trp147Arg). When examining affected children's family members, 41 people with heterozygous carriage of the GALNS gene were identified: MPS 3, MPSII-12, MPSIVA-26, relatively. In one sibling of the index patient with Morquio syndrome (MPSIVA) c.463G>T (p.Gly155Cys) mutation was found in the homozygous state. Obtained experimental results allow doctors to direct patients to proper treatment as well as prophylactic activities with families including fetus prenatal diagnostics in the next pregnancies.

Keywords: Hurler syndrome, Hunter syndrome, Morquio syndrome, gene, missense mutation, enzyme

INTRODUCTION

Mucopolysaccharidosis (MPS) is a group of rare lysosomal storage inherited diseases. There are several types of disease that occur because of corresponding lysosomal enzyme activity deficiency and lead to damage of glycosaminoglycans (GAG) degradation (Caciotti et al., 2018; Zanetti et al., 2021). MPS I (Hurler syndrome, Hurler/Scheie, Scheie) occurs because of the alpha-L-iduronidase enzyme of the IDUA

gene, located in the short shoulder of Chromosome 4 in locus 4p16.3. Damage of alpha-L-iduronidase enzyme activity leads to dermatan sulfate and heparan sulfate storage in body cells and tissues. The heritage type is autosome recessive (AR). The frequency of disease among live newborns is 1:100 000-1.5:500 000. The fraction of MPS I among all MPS types consists of 15% (Martins et al., 2018; Puckett et al., 2021). MPS II (Hunter syndrome) arises because of iduronate-2-sulfatase lysosomal enzyme

deficiency. The given enzyme (IDS) is in the long shoulder of Chromosome X (Xq28). The heritage type is X-linked recessive (XR). Average populational frequency varies in the range of 1.5-2:100 000 live newborns.

Among all MPS patients, Hunter syndrome (MPS II) comprises 56% (Noh et al., 2014; Fenton-Navarro et al., 2017). Morquio syndrome (MPS IV) averagely consists of 10% of all affected with MPS diagnosis. The disease starts with a deficiency of two lysosomal enzymes: N-acetylgalactosamine-6-sulfatase (MPS IVA) and beta-galactosidase (MPS IVB) coded by GALNS and GLB1 genes, relatively. N-acetylgalactosamine-6-sulfatase activity deficiency leads to keratan sulfate storage. The ratio of frequencies MPS IVA/MPS IVB is 6/1. The inheritance type is AR. The prevalence average is 1.53-2:100000 live newborns. In developed countries, newborn neonatal screening is carried out for MPS complication rate (Hendriksz et al., 2015; Filocamo et al., 2018; Chien et al., 2020; Kubaski et al., 2020).

The goal of our research was the identification and study of the genetics of Hurler syndrome (MPS I), Hunter syndrome (MPS II), and Morquio syndrome (MPS IV) for patients from the population of the Azerbaijan Republic.

MATERIALS AND METHODS

Genetic research patients were revealed during medical genetic consultation of affected children with any clinical manifestations of mucopolysaccharidosis. Medical genetic examinations of patients were carried out in the presence of doctor pediatrician and doctor geneticist in children's medical centers in Baku, Gyandzhe cities as well as central clinics in Sheki-Zagatala, Guba-Khachmas, Lankaran-Astara, Shirvan and Mughan economical zones of Azerbaijan Republic. Nineteen affected children with clinical manifestations of Hurler syndrome (1 index patient), five index patients with Hunter syndrome, and thirteen index patients with Morquio syndrome. Fifty-four family members were also examined.

To confirm suspicious clinical manifestations, DNA-level genetic analysis was applied. A genetic study was carried out with the

GSN (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, IDS, GALC, SUMF1, GAA, GUSB, GBA1, GLB1, ARSB, PAH, SMPD1, ADGRV1 and PLA2G6. Sequencing of GALNS, IDUA, IDS, and GBA1 genes on the DNA level was identified with the NGS technique (Next Generation Sequencing). There were used the following kits and programs: kit - Lysosomal Storage Disease Kit, Celeomics®; Analysis Platform - MiSeq Sequencing, Illumina®; Analysis programme - SEQ analysis platform, GENOMIZE® (<http://seq.genomize.com>), GRCh37(h19) (Alizada and Rasulov, 2023).

“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 np).” The pathogeny classification of the obtained results was conducted correspondently to “Guidelines of ACMG®”.

RESULTS AND DISCUSSION

Our results of molecular genetic studies of affected children with Hurler, Hunter and Morquio diseases are presented in Table 1. There are presented types of mucopolysaccharidoses syndromes as well as genes, mutation types on gene and synthesized protein levels, gene pathogeny rate, and gene location in chromosome and its heritage type.

An affected kid with Hurler syndrome had got nucleotide change of Cytosine to Thymine in position 1882 of exon 1 in the IDUA gene in a homozygous state (c. 1882C>T/c. 1882C>T). In consequence of missense mutation/nonsense mutation in newly synthesized protein, a substitution occurred – Arginine amino acid changed with Tyrosine in position 628 (NP_000194.2: p. Arg628Ter). The parents of the affected kid were cousins.

Nevertheless, the population of the

Azerbaijan Republic and the Islamic Republic of Iran have intrinsic ethnic factors in subgroups, there were none among identified patients with Hurler syndrome having c. 1882C>T IDUA gene mutation. However, the given mutation was found among patients in the Republic of Turkey and was one of ten identified mutations of the IDUA gene (Church et al., 2013; Atçeken et al., 2016).

It was established that the most spread type of changes (56.9%) in the IDUA gene was missense mutation/nonsense mutation. The authors studied 292 IDUA genes and managed to find out the following mutation types: splicing - 15.8%, regulator -0.3%, small deletion, small insertion - 23.6%, large deletion, large insertion - 2.4%, complex rearrangements - 1% (Puckett Y. et al., 2021).

The description of Alshahran H. et al. (2023) for MPSI screening of 618 newborns in Kuwait was carried out in the course of 2021-2022 years to evaluate activity levels for the alpha-L-iduronidase enzyme.

Enzyme deficiency was stated to be present in 20 newborns. Molecular study of newborns with enzyme deficit identified IDUA gene c.1882C>T mutation. The frequency of MPS I in the USA was 0.29:100,000 live newborns. In some countries of the world neonatal screening of newborns is being held for the presence of MPSI (Hendriksz et al., 2015; Galimberti et al., 2018).

Three mutations of the IDS gene were identified in five patients during our studies. They had been diagnosed with MPS II: c. 1106C>G (p. Asp358Leu), c. 322T>G (p. Asp358Leu) and c. 1215del (p. Leu*34406Phefs). There were two missense/nonsense mutations and one deletion.

F.Kubaski et al. (2020) in studies of 659 affected patients with Hunter syndrome stated the highest frequency of missense mutation/nonsense mutation of the IDS gene (49.8%). The rest mutation types were distributed as follows: splicing - 9.3%, regulator - 0%, small deletion, small insertion - 11.5%, large insertion, large deletion - 8.8%, complex re-arrangement - 3%.

Table 1. Identified IDUA, IDS, GALNS, and GLB1 gene mutations in the Azerbaijan population

MPS type	Gene, mutation	Protein	Pathogeny	Chromosome, Inheritance type
MPS I Hurler syndrome	IDUA: alpha-L-iduronidase NM_000203.5: c.1882 C >T; Exon 1	p.Arg628Ter	Pathogenic (class 2)	Chr 4p16.3, AR
MPS II Hunter syndrome	IDS: iduronate 2-sulfatase NM_000202.5: c.1215del	p.Leu*34406Phefs	Pathogenic (class 1)	Chr Xq28, X-R
MPS II Hunter syndrome	IDS: iduronate-2-sulfatase. NM_000202.5: c.322T>G	p.Tyr108Asp	Pathogenic (class 1)	Chr Xq28, X-R
MPS II Hunter syndrome	IDS: iduronate-2-sulfatase. NM_000202.5: c.1106C>G	p.Asp358Leu	Pathogenic (class 1)	Chr Xq28, X-R
MPS IVA Morquio syndrome	GALNS: N-acetyl galactosamine 6-sulfatase, NM_001323544.1: c.1144C>G	p.Leu382Val	Pathogenic (class 1)	Chr 16q24.3, AR
MPS IVB Morquio syndrome	GLB1 beta-galactosidase, NM_000404.4; c.176G-A; Exon	p.Arg59His	Pathogenic (class 1)	Chr 3p22.3, AR
MPS IVA Morquio syndrome	GALNS: N-acetyl galactosamine 6-sulfatase, ENST00000268695, c.1265A-G	p.Gln422Arg	Pathogenic (class 1)	Chr 16q24.3, AR
MPS IVA Morquio syndrome	GALNS:ENSG00000141012-NM-0011323543, c. 463G-T	p.Gly155Cys	Pathogenic (class 1)	Chr -16q24.3, AR
MPS IVA Morquio syndrome	GALNS:ENSG00000141012-ENST00000268695, c.1018 G-T	p.Gly340Cys	Pathogenic (class 1)	Chr -16q24.3, AR
MPS IVA Morquio syndrome	GALNS NM_001323544.1: c.157G>A	p.Gly53Arg	Pathogenic (class 1)	Chr -16q24.3, AR
MPS IVA Morquio syndrome	GALNS: NM_001323544.1: c.553C>T	p.Pro185Ser	Pathogenic (class 1)	Chr -16q24.3, AR
MPS IVA Morquio syndrome	GALNS:NM_001323544.1:c.443A>G Exon 5	p.His148Arg	Pathogenic (class 1)	Chr -16q24.3, AR
MPS IVA Morquio syndrome	GALNS:NM_001323544.1: c.1283A>G	p.Gln428Arg	Pathogenic (class 1)	Chr -16q24.3, AR
MPS IVA Morquio syndrome	GALNS:NM_001323544.1: c.439T>A	p.Trp147Arg	Pathogenic (class 1)	Chr -16q24.3, AR

When examining Taiwan specifically screening iduronate-2-sulfatase enzyme activity authors found 195 cases of the disease. At the same time, 140 asymptomatic cases were revealed. The genetical analysis stated 19 new mutations including c. 1106C>G (p. Asp358Leu) (Lin et al., 2009).

The genetic mutation c.322 T-G is also one of the many mutations linked with Hunter syndrome. This disease is faced mainly in male patients. It leads to damage to various parts of the human body. This mutation causes tyrosine-to-aspartic acid to change in position 108. That change damages the ability to break down GAGs.

The following statistics may be observed if we analyzed the prevalence of Hunter syndrome globally: the United States ranked first in terms of Hunter syndrome cases until 2017. There were 503 cases of the said syndrome. The second place was given to Japan (309 cases). It is known that Asian countries such as Japan, China, Korea, and Taiwan have relatively high severity of Hunter syndrome. The severity could vary. The next are five countries of the European Union: the United Kingdom, Spain, Italy, Germany, and France. The data available for now is known as dated back to 2017, not later. For those days, Germany had the most frequency of identified cases (83 people) followed by the United Kingdom (68 cases).

Genetical analysis of the GALNS gene for 13 affected children with clinical manifestations of Morquio syndrome resulted in the following nine mutations: c. 1144C>G (p. Leu382Val), c. 1265A-G (p. Gln422Arg), c. 463G-T (p. Gly155Cys), c. 1018G-T (p. Gly340Cys), c. 157G>A (p. Gly53Arg), c. 553C>T (p. Pro185Ser), c. 443A>G (p. His148Arg), c. 1283A>G (p. Gln428Arg), c. 439T>A (p. Trp147Arg). All nine GALNS gene mutations had missense mutations. The clinical variety of Morquio syndrome in patients from the Azerbaijan Republic could be explained by the GALNS gene mutation variety. In one patient, the GLB1 gene was identified with its mutation c. 176G>A (p. Arg59His).

At the same time, we consulted and analyzed genetically 41 people with heterozygous carriage: MPS I-3 people, MPS II-12 people, MPS IV-26 people, relatively. One sibling was found to have a GALNS gene mutation: c. 463G-T (p. Gly155Cys) in the homozygous state (MPS

IVA).

Our studies revealed gene level one mutation type - missense mutation/nonsense mutation in all affected children with MPS IVA and MPS IVB, that was the most spread mutation types. F.Kubaski et al., 2020 found that in genetical studies of patients with MPS I and MPS II syndromes in both genes: GALNS и GLB1 missense mutation/nonsense mutation type prevailed as 74.4% and 76%, relatively. The authors at that time examined 556 cases. The second mutation type for MPS IV both types was large deletion/large insertion 11.5% and 15.4%, relatively. Small deletion/small insertion takes the third position: 9.8% and 7.3%.

GALNS mutations' heterozygosity explains the vast clinical variability of MPS IVA. More than 300 mutations of the gene are identified and described, they are as follows: 78.4% are linked with missense mutations, 9.2% with small deletions, 5.0% with nonsense mutations, 2.4% with large deletions, 1.6% with insertions, small and large deletions, and transversions (Hendriks, C. J. et al., 2015). The incidence of Morquio syndrome in different populations varies. When screening infants in Sweden and Japan between 1982 and 2009, Khan et al. (2017) discovered and diagnosed 469 affected patients with MPS of all forms, resulting in a frequency of 1.5:100,000 live newborns. MPS II accounted for 55% of them (0.8:100 000). MPS I and MPS II were shown to occur 15% and 10% of the time, respectively. In Sweden, retrospective epidemiological analysis was carried out for a period of 34 years, where genetic analyses of 41 patients were run. 12% of patients had got MPS I diagnosis, and 24% had MPS IV. In populations of Eastern Asia, Germany, Northern Ireland, Portugal and the Netherlands, MPS II prevailed highly up to 50%. It should be mentioned that in the above enumerated countries, other MPS types were also widespread. Differing from those said countries epidemiological data in Turkey showed quite a distinguished picture. 339 affected people with MPS diagnoses were distributed in the following order: MPS I -7.79%, MPS II - 14.29%, MPS III - 28.57%, MPS IV - 28.57%, MPS VI - 18.48%, and MPS VII - 1.29%. In Turks residing in Germany two types of MPS were found: MPS IIIB -33% and MPS IV -22. There were screenings of live newborns in the

USA for 20 years, and the frequency consisted of 0.98:100 000. Around 2.67 affected kids in every million newborns. The frequency of MPS I, MPS II and MPS III prevailed (0,26:100 000 and 0,70-0,71). Frequency of MPS IV, MPS VI and MPS VII were lower - 0.14, 0.04 and 0.02, relatively, i.e. per 100,000 live newborns (Church et al., 2013; Chen et al., 2016; Atçeken et al., 2016; Khan. et al., 2017; Caciotti et al., 2018; Puckett 2021; Zanetti et al., 2021).

CONCLUSION

Hence, when medical genetical consultation of affected patients suspicious of lysosomal storage diseases, especially mucopolysaccharidoses, we for the first time in the Azerbaijan population identified and genetically studied 19 affected patients and 54 of their family members. One index patient suspicious with Hurler syndrome (MPS I) was identified missense mutation of the IDUA gene (NP_000194,2: c. 1882C>T, p. Arg628Ter) in the homozygous state. Three mutations of the IDS gene were identified: two missense mutations 1106C>G (p. Asp358Leu), c.322T>G (p. Asp358Leu) and one deletion c.1215del (p. Leu*34406Phefs) in hemizygous. In patients with Morquio syndrome (MPS IVA), nine GALBS gene missense mutations were identified: c. 1144C>G (p. Leu382Val), c. 1265A-G (p. Gln422Arg), c. 463G-T (p. Gly155Cys), c. 1018 G-T (p. Gly340Cys), c. 157G>A (p. Gly53Arg), c. 553C>T (p. Pro185Ser), c. 443A>G (p. His148Arg), c. 1283A>G (p. Gln428Arg), c. 439T>A (p. Trp147Arg) and one missense mutation of the GLB1 gene - c. 176G-A (p. Arg59His) that was responsible for Morquio syndrome (MPS IVB). Identified missense mutations were in homozygous and double heterozygous (compound) states. When examining family members of affected index patients, we found 41 people with heterozygous carriage of genes: 3 people with IDUA gene (MPS I) carriage, 12 people with IDS gene (MPS II) carriage, 26 people with GALNS gene (MPS IVA) carriage. At the same time when examining family members, a sibling of an index patient with Morquio syndrome (MPS IVA) identified c. 463G-T (p. Gly155Cys) in a homozygous state.

Considering the reproductive age of parents, fetus prenatal diagnostics is being planned for the next pregnancies.

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ORCID:

- Sevda Alizada: <https://orcid.org/0000-0002-7543-0094>
Shirkhan Musayev: <https://orcid.org/0000-0002-8308-7089>
Elkhan Rasulov: <https://orcid.org/0000-0003-1363-1648>