Determination of the Population Allelic Frequency of the Variants of the MPS Complex in Southwestern Colombia

Journal of Inborn Errors
of Metabolism & Screening
2021, Volume 9: e20210021
DOI: https://doi.org/10.1590/2326–4594–
JIEMS–2021–0021

Lina Johanna Moreno Giraldo[1,2,3,4], José María Satizabal[1,2,4] and Adalberto Sánchez Gómez[1,2,4]

Abstract

Mucopolysaccharidoses are lysosomal storage diseases characterized by the excessive accumulation of glycosaminoglycan sulfate in organs and tissues. To determine the population allelic frequency of the MPS complex variants in a population without clinical and molecular diagnosis of MPS. An observational descriptive study was carried out where the allelic frequency of variants presents in the IDUA, IDS, SGSH, NAGLU, HGSNAT, GNS, GALNS, GLB1, ARSB, GUSB, HYAL1 genes was determined by means of the sequencing of 320 exomes from patients without a clinical diagnosis of MPS; the results were tabulated, and allelic frequency formulas were used to determine the values associated with each of the genes. 509 alleles associated with the MPS complex were reported, of which 262 have not been previously reported. Genes with the most frequent allelic presence were IDUA, GLB1 and GALNS, involved in MPS I and MPS IV A / B. The total frequencies ranged between 0.00393 (2 alleles) and 0.47937 (248 alleles). These studies make it possible to determine polymorphisms that circulate in the country, present in patients not affected with MPS, allowing to expand the knowledge about the characteristics of the alleles that are present in affected patients.

Keywords: Computational Biology, Exome sequencing, Mucopolysaccharidosis Complex, Lysosomal Storage Diseases, Allelic Frequency.

Introduction

Mucopolysaccharidosis complex (MPS) is a group of orphan diseases - rare, of low prevalence, characterized by the deficiency of enzymes involved in the metabolism of glycosaminoglycans (GAGs) at lysosomal level [1]. It is characterized by intracellular GAG accumulation, producing alterations of multiple organs and systems. The clinical presentation in patients with MPS includes multisystemic affectation, mainly the liver, the spleen, the central nervous system, bone, cartilages, eyes and, when stored in excessive quantities, developmental problems, skeletal abnormalities, cervical myelopathy, and spinal cord compression, defects in the immune and neural systems and death at an early age are presented [2, 3].

Seven different types of MPS disorders are recognized (I, II, III, IV, VI, VII, and IX) with 11 specific lysosomal enzyme deficiencies. All types of MPS have an autosomal recessive mode of inheritance, except for MPS II (Hunter syndrome), which is X-linked recessive inherited, and therefore, affects males primarily [4]. Overall, the prevalence is 1.04 to 4.8/100,000 births, varying by country, region, or ethnic background [5].

In Colombia, the study conducted by Gómez *et al.* (2012) estimated that the combined frequency of all MPS cases is 1.98 cases per 100,000 live births, with type IV being the highest frequency with 0.68 per 100.000 live births; they also proposed an incidence of 0.45:100,000 (VN) in patients with MPS I; 0.17:100,000 (VN) in MPS III; 0.68:100,000 (VN) in MPS IVA; 0.23:100,000 (VN) in patients with MPS VI; there were no incidences reported for MPS VII and MPS IX. Considering data until 2012, the authors also determined that in Colombia,

[1] Universidad del Valle, Facultad de Salud, Cali, Valle del Cauca, Colombia.
[2] Universidad Santiago de Cali, Valle del Cauca, Colombia.
[3] Universidad Libre, Cali, Valle del Cauca, Colombia.
[4] Universidad del Valle, Grupo de Enfermedades Congénitas del Metabolismo, Cali, Colombia.

Received April 25, 2021, and in revised form May 20, 2021. Accepted for publication July 05, 2021.

Corresponding Author:
Lina Johanna Moreno Giraldo, E-mail: linajohannamoreno@yahoo.es

MPS IVA or Morquio A syndrome has a frequency of 0.68 cases per 100.000 live births, with MPS being more frequent in the Colombian population [6].

According to the report of the weekly epidemiological bulletin 05 for the epidemiological week from January 27th to February 2nd in 2019, Colombia, the prevalence of MPS IV was presented with a sample size of approximately 150 patients, corresponding to 0.3:100,000 inhabitants. For the epidemiological period IV of 2020, the ratio of notification for MPS II was 7 cases (0.15%), and MPS VI was 6 cases (0.13%) [7, 8].

In Colombia, it is difficult to measure the frequency of these diseases because only the most severe cases are generally diagnosed, being few mild cases or mutation carriers diagnosed [9, 10]. For this reason, studies providing complete and updated information associated with the population's allele frequencies of mutations present in the southwestern Colombian population are required. Those will allow the medical community and health authorities the early identification and establishment of diagnosis programs considering that nowadays specific treatment is found for several of them, joint to the importance of the transdisciplinary handling that minimizes the morbidity - mortality attributed to this pathological complex, including appropriate genetic advice and search of possible directed therapeutic targets, allowing an approach to precision medicine.

Methods

Type of Study

A descriptive observational study in which the allele frequency of variants identified in the genes IDUA, IDS, SGSH, NAGLU, HGSNAT, GNS, GALNS, GLB1, ARSB, GUSB, and HYAL1, was determined in patients without a clinical diagnosis of MPS. This study is guided by the MPS studies approved in the institutional ethics committee No 016-016, Universidad del Valle.

Study Population

For the present study, the results gathered from the complete exome sequencing of 320 patients without a clinical diagnosis of MPS from the Southwestern Colombian region, belonging to the database of the 'Instituto de Genética Médica' - GENOMICS (Cali), were taken after signing the consent and informed assent.

Exome Sequencing

Blood extraction was performed and subsequent collection on filter paper and immersion in phosphate buffer. DNA extraction using Qiagen's DNeasy package. Each sample was quantified, and the DNA quality and quantity were verified. Afterward, massive sequencing of Nextera TM libraries was performed using the Illumina platform with 100X coverage. Alignment with GRCh38 reference genome. The new generation sequencing platform used was Illumina. Modified nucleotides with specific fluorescent labels were used, which presented a chemical modification (reversible terminators) that avoids the union of more than one labeled nucleotide in each reaction site in such a way that it can locate the one that corresponds to each point in the sequence and reducing the risk of errors in the sequencing. The instrument used was HiSeq 2500 machine, with a reading length (2 x 150 bp), total bases per sequencing: 450-500 Gb, number of readings (cycles) performed (million) 4000, and coverage 100 X. The sequencing results were obtained in VCF files and passed through the first filter of interpretation and prioritization. The annotations include medicament associations TARGET, 1000 genomes, Exome Variant Server, and Exome Aggregation Consortium (ExAC), minor alleles frequencies per population. Variant zygosity, accumulation coverage, and variant allele frequencies are provided when users send VCF files. Variant and gene-level annotations and bioinformatics scores were provided to allow interpretation and prioritization of variants identified in sequencing studies, which included reading frame displacement, insertions/deletions, splice site, missense, and nonsense.

Calculation of Allele Frequencies

Through the findings of VCFs, variants in the genes associated with the MPS complex were searched. For each one of the variants found, it was tabulated its position, change of nucleotide, change of amino acid, and allele frequency. The allele frequency is the measure of the relative proportion of alleles in each population, expressed in percentage or in the unit. It is estimated by counting the number of times the allele is observed at a locus and dividing it by the total number of alleles studied.

The gene-allele frequency will be calculated by simple count:

$$f(A) = \#\text{ alleles observed} / \#\text{ total alleles}$$

Inclusion Criteria

Exome results from patients with complex diseases that are different from MPS., obtained from the database of the 'Instituto de Genética Médica' – GENOMICS (Cali).

Exclusion Criteria

Exome results from patients who have not signed the respective informed consent - assent to sample collection and use of data.

Bioethical Aspects

- Protection of people and animals: The authors state that the procedures followed conformed to the ethical standards of responsible human experimentation committee and are aligned to the principles set out in the Declaration of Helsinki of the World Medical Association (WMA); the level of this research has been categorized as minimal risk since it presents a low risk of

physical harm to the participant as it is a retrospective study of review results.

- Confidentiality of the data: The authors state that no patient data appear in this article and they have followed their work center's protocols.
- Right to privacy and informed consent: The authors declare that in this article there is no personal data of patients and the respective consent and informed assent was obtained for the processing of samples and use of data in a confidential manner by the patient's legal representative.

Results

When obtaining the results of the sequencing of complete exomes in 320 patients without a clinical diagnosis of MPS with suspicion of complex diseases, each one of the data was tabulated, noting the alleles observed for each locus concentrating the data to subsequently obtain the allele frequencies of each one of them. The data was organized according to the change of nucleotide, amino acid, and allele frequency in Table 1.

The alleles found in each one of the genes that compose the MPS complex presented different distributions of allele frequencies (Figure 1), which are detailed below.

Specifically, for the IDUA gene associated with MPS I, 121 alleles were identified of which the changes with the highest frequencies were p.His33Gln (0.32809), the T>C transition located in position Chr4:983060 (0.31434), the A>G transition located in position Chr4:985727 (0.28880), and the C>T transition located in position Chr4:983809 (0.24558), all these alleles have been associated with benign phenotypes and are not reported in patients presenting the disease.

For the IDS gene related to MPS II, 12 alleles were identified. Among the most frequent for this group, it was reported the one found in the synonym mutation p.Thr146=, identified with a frequency of 0.10806. Followed, the change G>GA was in ChrX:14852574, with a frequency of 0.01768. And the transitional change C>A was in ChrX:148586711, with a frequency of appearance of 0.01572.

Concerning the genes associated with MPS III, 47 alleles associated with the SGSH gene were found. It is emphasized the presence of the change p.Val361Ile found in 163/320 patients with a frequency of 0.32024, the intronic variants 663+17T>C and 250-26C>T reported with a frequency of 0.29470 and 0.23576 respectively, and the synonym variant p.Arg820Trp that presented an allele frequency of 0.17682. For the NAGLU gene, 36 allele variants were found; the synonym allele p.Ser141= showed a frequency of 0.36149. Likewise, the alleles 531+50G>C, p.Arg737Gly, and the change T>C located in Chr17:40699332, presented frequencies 0.33399, 0.34971, and 0.35560, respectively. In the HGSNAT gene, 27 allele variants were found. Of these, the ones that showed a higher frequency were p.tyr583= (0.36346) and the alleles, located in Chr8: 43033368, consistent with the

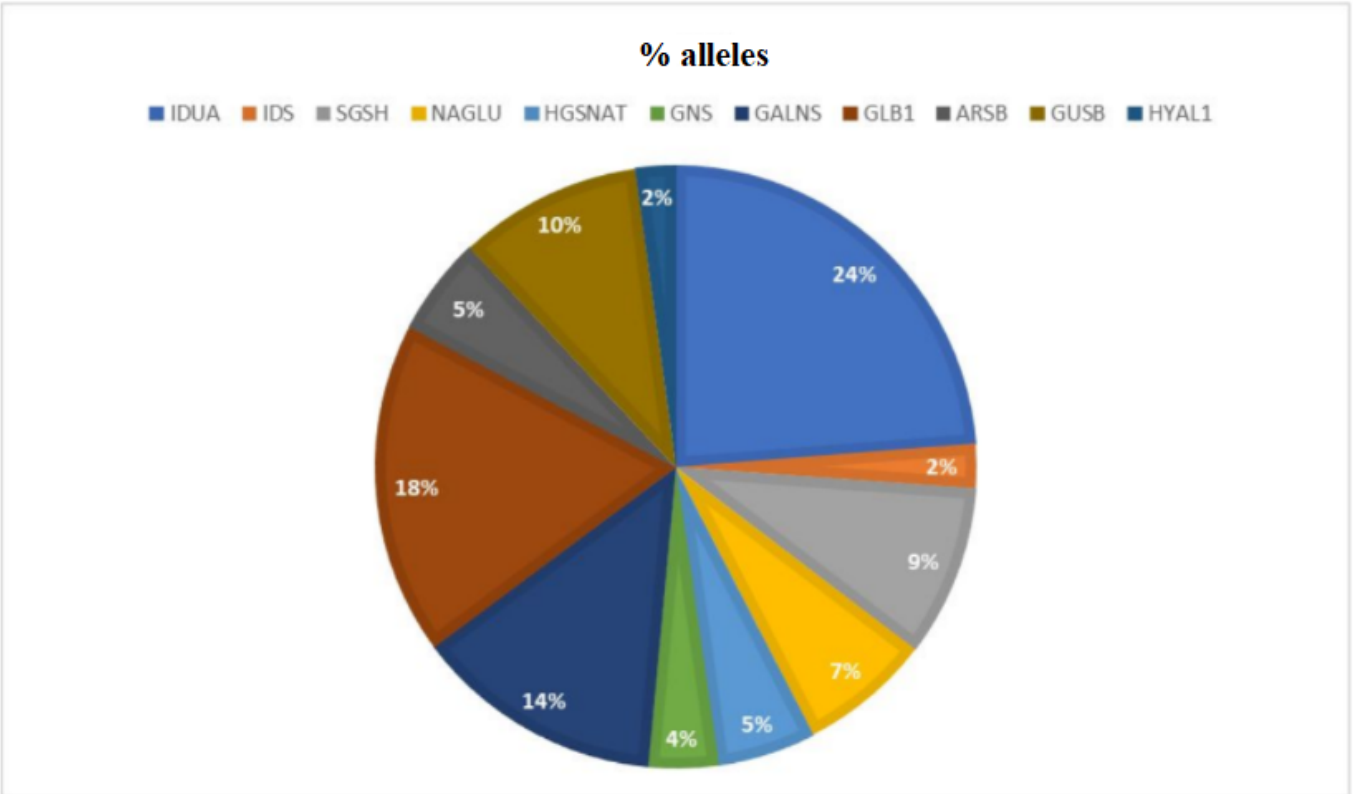

Figure 1. Percentage of alleles found in genes associated with the MPS complex.

Table 1. Allelic frequency found in gene variants associated with the MPS complex.

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	IDUA	Chr4: 980664	C>A		0,01179
	IDUA	Chr4:980828	C>A		0,00393
	IDUA	Chr4:980841	C>A		0,00393
	IDUA	Chr4:980865	G>A		0,00393
	IDUA	Chr4:980883	11T>C	p.Leu4Pro	0,00393
	IDUA	Chr4:980896	24C>A	p.Ala8=	0,21807
	IDUA	Chr4:980932	60G>A	p.Ala20=	0,21415
	IDUA	Chr4:980971	99T>G	p.His33Gln	0,32809
	IDUA	Chr4:980987	c.115G>A	p.Ala39Thr	0,00393
	IDUA	Chr4:981077	C>A		0,00393
	IDUA	Chr4:981546	C>A		0,00393
	IDUA	Chr4:981550	C>A		0,00393
	IDUA	Chr4:981564	C>A		0,00393
	IDUA	Chr4:981597	C>A		0,00393
	IDUA	Chr4:981673	235G>A	p.Ala79Thr	0,00393
	IDUA	Chr4:981684	246C>G	p.His82Gln	0,00393
	IDUA	Chr4:981746	C>A		0,00393
	IDUA	Chr4:981752	G>A		0,00393
	IDUA	Chr4:981786	C>A		0,00393
	IDUA	Chr4:982635	C>A		0,00982
	IDUA	Chr4:982736	C>G		0,00393
	IDUA	Chr4:982756	C>A		0,00393
MPS I - Hurler syndrome	IDUA	Chr4:982784	C>A		0,00393
	IDUA	Chr4:982812	C>A		0,00393
	IDUA	Chr4:982814	C>A		0,00393
	IDUA	Chr4:982852	G>A		0,21415
	IDUA	Chr4:982913	G>C		0,00393
	IDUA	Chr4:982985	C>A		0,00393
	IDUA	Chr4:983014	G>C		0,00982
	IDUA	Chr4:983060	T>C		0,31434
	IDUA	Chr4:983130	G>T		0,00393
	IDUA	Chr4:983139	C>A		0,00393
	IDUA	Chr4:983178	1549G>A	p.Gly517Arg	0,00393
	IDUA	Chr4:983183	C>T		0,00393
	IDUA	Chr4:983197	G>A		0,00393
	IDUA	Chr4:983216	C>T		0,00196
	IDUA	Chr4:983254	C>A		0,00393
	IDUA	Chr4:983280	G>A		0,00393
	IDUA	Chr4:983296	G>A		0,00393
	IDUA	Chr4:983314	C>T		0,00786
	IDUA	Chr4:983316	C>A		0,00393
	IDUA	Chr4:983323	C>A		0,00393
	IDUA	Chr4:983331	T>C		0,00393
	IDUA	Chr4:983342	C>T		0,00393
	IDUA	Chr4:983550	A>G		0,00393
	IDUA	Chr4:983574	C>T		0,00393

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	IDUA	Chr4:983612	1115G>A	p.Arg372His	0,01179
	IDUA	Chr4:983625	C>T		0,02358
	IDUA	Chr4:983668	G>A		0,00393
	IDUA	Chr4:983716	C>A		0,00393
	IDUA	Chr4:983777	G>T		0,00393
	IDUA	Chr4:983797	C>A		0,00393
	IDUA	Chr4:983809	C>T		0,24558
	IDUA	Chr4:983854	C>T		0,00393
	IDUA	Chr4:983857	C>A		0,00393
	IDUA	Chr4:983898	C>T		0,00982
	IDUA	Chr4:983920	C>A		0,00393
	IDUA	Chr4:983941	G>A		0,00393
	IDUA	Chr4:983944	C>T		0,00393
	IDUA	Chr4:983967	G>A		0,00393
	IDUA	Chr4:984022	C>A		0,00393
	IDUA	Chr4:984086	C>A		0,00393
	IDUA	Chr4:984101	T>C		0,00393
	IDUA	Chr4:84111	A>G		0,00393
	IDUA	Chr4:984958	G>A		0,00786
	IDUA	Chr4:984963	C>A		0,00393
	IDUA	Chr4:984979	G>A		0,00786
	IDUA	Chr4:985003	G>A		0,00393
	IDUA	Chr4:985032	G>T		0,00982
MPS I - Hurler syndrome	IDUA	Chr4:985180	C>T		0,01375
	IDUA	Chr4:985261	C>A		0,00786
	IDUA	Chr4:985321	C>T		0,00196
	IDUA	Chr4:985330	G>A		0,00393
	IDUA	Chr4:985338	C>A		0,00393
	IDUA	Chr4:985356	C>A		0,00393
	IDUA	Chr4:985369	G>C		0,01375
	IDUA	Chr4:985372	C>T		0,00786
	IDUA	Chr4:985436	C>A		0,01572
	IDUA	Chr4:985445	G>T		0,00393
	IDUA	Chr4:985462	C>A		0,01179
	IDUA	Chr4:985465	C>G		0,00786
	IDUA	Chr4:985468	C>A		0,00393
	IDUA	Chr4:985475	T>A		0,03536
	IDUA	Chr4:985727	A>G		0,28880
	IDUA	Chr4:985994	C>G		0,00196
	IDUA	Chr4:994452	352C>T	p.Leu118=	0,23379
	IDUA	Chr4:994526	C>A		0,00589
	IDUA	Chr4:994662	T>C		0,00393
	IDUA	Chr4:995305	543T>C	p.Asn181=	0,07662
	IDUA	Chr4:995422	590-45G>A		0,07662
	IDUA	Chr4:995459	590-8C>T		0,07269
	IDUA	Chr4:995820	G>A		0,01572
	IDUA	Chr4:995868	891C>T	p.Asn297=	0,03143

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	IDUA	Chr4:995908	C>A		0,00393
	IDUA	Chr4:995919	942G>C	p.Ala314=	0,06090
	IDUA	Chr4:995997	972+48A>G		0,06090
	IDUA	Chr4:996912	973-45G>C		0,06483
	IDUA	Chr4:996068	G>A		0,01768
	IDUA	Chr4:996165	1081G>A	p.Ala361Thr	0,07662
	IDUA	Chr4:996231	C>A		0,00393
	IDUA	Chr4:996248	1164G>C	p.Thr388=	0,04519
	IDUA	Chr4:996250	C>A		0,00786
	IDUA	Chr4:996258	1174C>T	p.Leu392=	0,00393
	IDUA	Chr4:996489	C>G		0,00786
	IDUA	Chr4: 996501	1190-10delC		0,01375
	IDUA	Chr4:996513	C>T		0,00786
MPS I - Hurler syndrome	IDUA	Chr4:996550	A>G		0,00982
	IDUA	Chr4:996555	1225G>C	p.Gly409Arg	0,00982
	IDUA	Chr4:996560	1230C>G	p.Thr410=	0,06287
	IDUA	Chr4:996576	C>A		0,00982
	IDUA	Chr4:996690	1360G>A	p.Val454Ile	0,06680
	IDUA	Chr4:996762	C>A		0,03340
	IDUA	Chr4:996768	1402+36T>C		0,06090
	IDUA	Chr4:996837	C>A		0,01179
	IDUA	Chr4:996888	1467C>T	p.Arg489=	0,07466
	IDUA	Chr4:996941	C>A		0,00786
	IDUA	Chr4:996979	C>A		0,01965
	IDUA	Chr4:996986	1524+41G>T		0,04126
	IDUA	Chr4:997095	1525-38T>C		0,09234
	IDUA	Chr4:997190	1582C>G	p.Pro528Ala	0,00589
	IDUA	Chr4:997910	C>A		0,01768
	IDS	Chr X: 148564573	G>T		0,00393
	IDS	ChrX:148564648	G>T		0,00786
	IDS	ChrX: 148564703	1227G>A	p.Thr409=	0,00589
	IDS	ChrX:148582520	467C>A	p.Pro156Gln	0,00786
	IDS	ChrX:148582522	465T>A	p.Phe155Leu	0,00786
MPS II – Hunter Syndrome	IDS	ChrX:148582549	438C>T	p.Thr146=	0,10806
	IDS	ChrX:14852574	G>GA		0,01768
	IDS	ChrX:148583625	C>T		0,01179
	IDS	ChrX:148586546	G>A		0,00786
	IDS	ChrX:148586672	G>C		0,00589
	IDS	ChrX:148586711	C>A		0,01572
	IDS	ChrX:148586673	C>A		0,01179
	SGSH	Chr17:78178125	C>A		0,00786
	SGSH	Chr17:78178844	2409G>A	p.Thr803=	0,00786
MPS III - Sanfilippo A syndrome	SGSH	Chr17:78178893	2458C>T	p.Arg820Trp	0,17682
	SGSH	Chr17:78178905	C>A		0,00393
	SGSH	Chr17: 78178916	C>T		0,05108

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	SGSH	Chr17:78178931	2496C>T	pl.Leu832=	0,00393
	SGSH	Chr17:78178998	C>A		0,00786
	SGSH	Chr17:78180817	C>A		0,00196
	SGSH	Chr17:78180840	2763C>T	p.Ile921=	0,00982
	SGSH	Chr17:78181957	G>A		0,01179
	SGSH	Chr17:78181958	2829C>T	p.Gly943=	0,00786
	SGSH	Chr17:78181996	A>G		0,01375
	SGSH	Chr17:78182014	2885G>A	p.Arg962Gln	0,00589
	SGSH	Chr17:78182125	C>A		0,03143
	SGSH	Chr17:78184314	G>A		0,00393
	SGSH	Chr17:78184374	C>A		0,00393
	SGSH	Chr17:78184679	1081G>A	p.Val361Ile	0,32024
	SGSH	Chr17:78184702	T>C		0,00393
	SGSH	Chr17:78184711	G>A		0,00589
	SGSH	Chr17.78184713	C>A		0,00393
	SGSH	Chr17:78184761	G>A		0,00589
	SGSH	Chr17:78185953	C>A		0,00786
	SGSH	Chr17:78186077	746-4A>G		0,00982
	SGSH	Chr17:78187565	C>T		0,00589
	SGSH	Chr17:78187673	675C>T	p.Phe225=	0,00786
MPS III - Sanfilippo A syndrome	SGSH	Chr17: 78187720	664-36T>C		0,16503
	SGSH	Chr17:78187721	664-39_664-38delCT		0,12181
	SGSH	Ch17:78187734	664-50G>A		0,02161
	SGSH	Chr17:78187884	T>C		0,00786
	SGSH	Chr17:78187954	663+17T>C		0,29470
	SGSH	Chr17:78187993	G>T		0,00589
	SGSH	Ch17:78188028	G>A		0,00589
	SGSH	Chr17:78188794	C>T		0,01179
	SGSH	Chr17:78188963	250-26C>T		0,23576
	SGSH	Chr17:78190794	C>A		0,00589
	SGSH	Chr17:78191017	G>T		0,00786
	SGSH	Chr17:78191030	89-39G>A		0,03733
	SGSH	Chr17:78191036	89-45G>A		0,03733
	SGSH	Chr17:78193986	C>A		0,02358
	SGSH	Chr17:78194002	88+23C>G		0,00589
	SGSH	Chr17:78196622	C>A		0,00393
	SGSH	Chr17:78196612	C>A		0,00393
	SGSH	Chr17:78196506	C>A		0,00393
	SGSH	Chr17:78195371	G>T		0,00393
	SGSH	Chr17:78195366	T>G		0,00393
	SGSH	Chr17:78194160	G>A		0,00589
	SGSH	Chr17:78194084	G>C		0,00393
	NAGLU	Chr17:40688275	C>A		0,00393
	NAGLU	Chr17:40688327	C>A		0,01179
MPS III - Sanfilippo B syndrome	NAGLU	Chr17:40688359	C>A		0,01375
	NAGLU	Chr17:40688395	C>A		0,00589
	NAGLU	Chr17:40688426	G>T		0,00393

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	NAGLU	Chr17:40688445	T>C		0,00393
	NAGLU	Chr17:40688453	G>A		0,00589
	NAGLU	Chr17:40688477	G>T		0,00786
	NAGLU	Chr17:40688505	C>A		0,00589
	NAGLU	Chr17:40688544	C>T		0,00589
	NAGLU	Chr17:40688628	C>A		0,00786
	NAGLU	Chr17:40688688	C>A		0,00786
	NAGLU	Chr17:40688722	C>A		0,01375
	NAGLU	Chr17:40689453	421T>A	p.Ser141Thr	0,01768
	NAGLU	Chr17:40689455	423T>C	p.Ser141=	0,36149
	NAGLU	Chr17:40689613	531+50G>C		0,33399
	NAGLU	Chr17:40690500	675G>T	p.Leu225=	0,00393
	NAGLU	Chr17:40690646	C>A		0,00393
	NAGLU	Chr17:40690667	C>T		0,00393
	NAGLU	Chr17:40690792	764+19C>G		0,00786
MPS III - Sanfilippo B syndrome	NAGLU	Chr17:40690824	C>A		0,00589
	NAGLU	Chr17:40693136	933C>G	p.Ala311=	0,00393
	NAGLU	Chr17:40693239	T>C		0,00589
	NAGLU	Chr17:40695174	T>A		0,00589
	NAGLU	Chr17: 40695470	1446G>A	p.Arg482=	0,00393
	NAGLU	Chr17:40695812	1788C>T	p.Gly596=	0,00393
	NAGLU	Chr17:40695813	G>A		0,00393
	NAGLU	Chr17:40695922	C>A		0,00589
	NAGLU	Chr17:40695929	C>A		0,00786
	NAGLU	Chr17:40695953	C>A		0,00393
	NAGLU	Chr17:40696007	1983G>A	p.Lys661=	0,00393
	NAGLU	Chr17:40696233	2209C>G	p.Arg737Gly	0,34971
	NAGLU	Chr17:40699116	C>T		0,00393
	NAGLU	Chr17:40699291	G>A		0,23969
	NAGLU	Chr17:40699317	G>A		0,00393
	NAGLU	Chr17:40699332	T>C		0,35560
	HGSNAT	Chr8:42995588	G>A		0,00393
	HGSNAT	Chr8:42995614	C>A		0,00393
	HGSNAT	Chr8:42995639	C>A		0,00393
	HGSNAT	Chr8:42995653,	G>A		0,00393
	HGSNAT	Chr8:42995680	C>A		0,00393
	HGSNAT	Chr8:42995702	G>A		0,00393
	HGSNAT	Chr8:42995739	C>A		0,00393
MPS III - Sanfilippo C syndrome	HGSNAT	Chr8:42995747	G>A		0,00393
	HGSNAT	Chr8:42995811	C>T		0,04322
	HGSNAT	Chr8:43002090	G>A		0,00393
	HGSNAT	Chr8:43014181	A>G		0,00393
	HGSNAT	Chr8:43014187	C>T		0,00393
	HGSNAT	Chr8:43023066	C>T		0,01768
	HGSNAT	Chr8:43023066	CTT>C		0,00393
	HGSNAT	Chr8:43023066	CT>C		0,03536

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	HGSNAT	Chr8:43023124	C>A		0,00393
	HGSNAT	Chr8:43023140	C>A		0,00786
	HGSNAT	Chr8:43023152	C>T		0,00786
	HGSNAT	Chr8:43025706	C>A		0,00589
	HGSNAT	Chr8:43027474	C>T		0,00393
MPS III - Sanfilippo C syndrome	HGSNAT	Chr8: 43033368	C>A		0,01375
	HGSNAT	Chr8:43035648	G>A		0,03536
	HGSNAT	Chr8:43052839	1567A>C	p.Lys523Gln	0,00786
	HGSNAT	Chr8:4305353	1749T>C	p.tyr583=	0,36346
	HGSNAT	Chr8:43054644	1840G>A	p.Val614Ile	0,00786
	HGSNAT	Chr8:43054647	1843G>A	p.Ala15Thr	0,00589
	HGSNAT	Chr8:43054684	1880A>G	p.Tyr628Cys	0,00786
	GNS	Chr12:65110530	1650T>C	p.His550=	0,01572
	GNS	Chr12:65110582	1598G>A	p.Arg533His	0,00196
	GNS	Chr12:65116872	A>T		0,00196
	GNS	Chr12:65122816	A>G		0,00393
	GNS	Chr12:65130856	C>T		0,00393
	GNS	Chr12:65133282	G>A		0,00393
	GNS	Chr12:65136943	T>G		0,00393
	GNS	Chr12:65137136	G>A		0,00982
	GNS	Chr12:65139405	C>T		0,01179
MPS III - Sanfilippo D syndrome	GNS	Chr12:65141588	C>T		0,09037
	GNS	Chr12:65141707	253-10delT		0,00393
	GNS	Chr12:65141722	C>T		0,00393
	GNS	Chr12:65146439	C>T		0,00393
	GNS	Chr12:65146532	198G>A	p.Pro66=	0,22593
	GNS	Chr12:65150485	C>T		0,30255
	GNS	Chr12:65150526	G>A		0,03733
	GNS	Chr12:65152901	G>C		0,01179
	GNS	Chr12:65153036	21C>G	p.Ala7=	0,01179
	GNS	Chr12:65153038	C>A		0,02947
	GALNS	Chr16:88884378	C>T		0,00393
	GALNS	Chr16:88884459	1438G>T	p.Val480Phe	0,00393
	GALNS	Chr16:88884466	1431G>A	p.Glu477=	0,22200
	GALNS	Chr16:88884484	1413C>T	p.Val471=	0,00393
	GALNS	Chr16:88884521	1376C>T	p.Ala459Val	0,00393
	GALNS	Chr16:88888955	C>A		0,00393
	GALNS	Chr16:88889083	1278G>T	p.Gly426=	0,00393
MPS IV - Morquio A syndrome	GALNS	Chr16:88889163	C>T		0,02358
	GALNS	Chr16:88824853	1156C>T	p.Arg386Cys	0,00196
	GALNS	Chr16:88891139	G>A		0,04519
	GALNS	Chr16:88891146	1242+29G>A		0,00589
	GALNS	Chr16:88891240	1177G>T	p.Ala393Ser	0,04519
	GALNS	Chr16:88893095	A>T		0,00393
	GALNS	Chr16:88893125	C>A		0,00393
	GALNS	Chr16:88893288	G>A		0,00196

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	GALNS	Chr16:88893295	T>C		0,00786
	GALNS	Chr16:88898507	901G>T	p.Gly301Cys	0,00393
	GALNS	Chr16:88901579	898+42G>C		0,03733
	GALNS	Chr16:88901594	C>T		0,00393
	GALNS	Chr16:88901596	898+25C>G		0,03733
	GALNS	Chr16:88901673	846C>T	p.Phe282=	0,04126
	GALNS	Chr16:88902111	758+22C>T		0,03733
	GALNS	Chr16:88902183	708C>T	p.His236=	0,15717
	GALNS	Chr16:88902199	692C>G	p.Ala231Gly	0,03733
	GALNS	Chr16:88902276	634-19G>A		0,15914
	GALNS	Chr16:88902277	634-20C>T		0,07662
	GALNS	Chr16:88902643	599C>T	p.Thr200Met	0,01572
	GALNS	Chr16:88903999	C>T		0,00393
	GALNS	Chr16:88904019	G>A		0,00393
	GALNS	Chr16:88904020	566+10C>T		0,00393
	GALNS	Chr16:88904086	510T>C	p.Tyr170=	0,04126
	GALNS	Chr16:88904166	C>A		0,00393
	GALNS	Chr16:88904210	C>A		0,00393
	GALNS	Chr16:88904220	C>A		0,00393
	GALNS	Chr16:88904222	C>A		0,00393
	GALNS	Chr16:88907499	T>C		0,00393
	GALNS	Chr16:88907516	G>A		0,00393
MPS IV - Morquio A syndrome	GALNS	Chr16:88907553	C>A		0,00393
	GALNS	Chr16:88908306	318C>T	p.Asn106=	0,01572
	GALNS	Chr16:88908418	G>A		0,00393
	GALNS	Chr16:88909065	c.244+49C>T		0,00982
	GALNS	Chr16:88909081	C>A		0,00393
	GALNS	Chr16:88909086	C>T		0,00393
	GALNS	Chr16:88909095	244+19C>T		0,07859
	GALNS	Chr16:88909118	240G>A	p.Ser80=	0,00393
	GALNS	Chr16:88909159	199C>A	p.Leu67Met	0,02358
	GALNS	Chr16:88909161	C>T		0,00393
	GALNS	Chr16:88909445	T>C		0,01375
	GALNS	Chr16:88909446	C>T		0,00393
	GALNS	Chr16:88909494	T>G		0,00393
	GALNS	Chr16:88921634	G>G		0,17092
	GALNS	Chr16:88921925	C>A		0,00393
	GALNS	Chr16:88922603	G>A		0,00786
	GALNS	Chr16:88922630	T>C		0,01179
	GALNS	Chr16:88923157	C>A		0,00786
	GALNS	Chr16:88923377	-92T>C		0,00982
	GALNS	Chr16:88923391	C>A		0,03340
	GALNS	Chr16:88923505	C>A		0,00393
	GALNS	Chr16:88923669	T>C		0,00393
	GALNS	Chr16:88925112	A>G		0,00393
	GALNS	Chr16:88926089	A>G		0,04715

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	GALNS	Chr16:88926388	C>T		0,02358
	GALNS	Chr16:88926412	C>G		0,01179
	GALNS	Chr16:88926432	G>A		0,00786
MPS IV - Morquio A syndrome	GALNS	Chr16:88926633	C<T		0,01179
	GALNS	Chr16:88926725	C>A		0,01572
	GALNS	Chr16:88927312	C>T		0,01768
	GALNS	Chr16:88927314	C>T		0,01572
	GLB1	Chr11: 134146536	C>T		0,02161
	GLB1	Chr11:134146643	C>A		0,00589
	GLB1	Chr11:134146680	G>A		0,00786
	GLB1	Chr11:134147095	C>G		0,00786
	GLB1	Chr11:134147151	CT>C		0,01572
	GLB1	Chr11:134147154	C>G		0,00786
	GLB1	Chr11:134147336	C>A		0,00589
	GLB1	Chr11:134147600	T>C		0,01572
	GLB1	Chr11:134147603	G>T		0,00196
	GLB1	Chr11:134147716	G>A		0,00393
	GLB1	Chr11:134147792	C>A		0,00393
	GLB1	Chr11:134151949	G>T		0,00393
	GLB1	Chr11:134151975	G>C		0,25147
	GLB1	Chr11:134151983	T>C		0,00393
	GLB1	Chr11:134158745	A>G		0,08251
	GLB1	Chr11:134158780	A>C		0,00786
	GLB1	Chr11:134175069	T>C		0,00196
	GLB1	Chr11:134179555	G>T		0,00196
	GLB1	Chr11:134179557	G>T		0,00393
MPS IV - Morquio A síndrome B	GLB1	Chr11:134179644	T>C		0,00393
	GLB1	Chr11:134179686	C>T		0,01179
	GLB1	Chr11:134181022	G>T		0,00393
	GLB1	Chr11:134182253	C>A		0,00196
	GLB1	Chr11:134182345	G>A		0,00393
	GLB1	Chr11:134182353	C>A		0,00393
	GLB1	Chr11:134182360	G>C		0,00393
	GLB1	Chr11:134182370	A>G		0,00393
	GLB1	Chr11:134182374	C>A		0,00393
	GLB1	Chr11:134182375	G>A		0,35167
	GLB1	Chr11:134183290	G>A		0,00589
	GLB1	Chr11:134184235	C>A		0,00982
	GLB1	Chr11:134184263	C>A		0,00786
	GLB1	Chr11:134188542	T>C		0,22790
	GLB1	Chr11:134188851	A>T		0,01375
	GLB1	Chr11:134188851	A>AT		0,47937
	GLB1	Chr11:134201912	G>T		0,00982
	GLB1	chr11:134201992	A>G		0,00589
	GLB1	Chr11: 134202036	C>T		0,09430
	GLB1	Chr11:134212766	C>A		0,00982

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	GLB1	Chr11:134212821	C>A		0,00982
	GLB1	Chr11:134212829	T>C		0,00393
	GLB1	Chr11:134214326	C>G		0,01179
	GLB1	Chr11:134226201	C>T		0,00393
	GLB1	Chr11:134226244	G>A		0,00393
	GLB1	Chr11:134226278	C>T		0,04322
	GLB1	Chr11:134226291	A>G		0,02947
	GLB1	Chr11:134229010	G>A		0,00786
	GLB1	Chr11:134229016	C>A		0,00589
	GLB1	Chr11:134234269	A>G		0,00786
	GLB1	Chr11:134237113	C>A		0,19253
	GLB1	Chr11:134237116	G>C		0,00393
	GLB1	Chr11:134237192	G>T		0,00393
	GLB1	Chr11:134238569	C>T		0,00393
	GLB1	Chr11:134238599	C>T		0,01179
	GLB1	Chr11:134238603	G>A		0,03340
	GLB1	Chr11:134239760	C>T		0,00786
	GLB1	Chr11:134240213	C>T		0,00393
	GLB1	Chr11:134240949	T>C		0,01768
	GLB1	Chr11:134241248	C>A		0,00589
	GLB1	Chr3:33055688	1594A>G	p.Ser532Gly	0,01768
	GLB1	Chr3:33055705	1577G>A	p.Gly526Asp	0,00393
MPS IV - Morquio A síndrome B	GLB1	Chr3:33055721	1561C>T	p.Arg521Cys	0,36149
	GLB1	Chr3:33055849	A>G		0,00393
	GLB1	Chr3:33058254	1426C>T	p.Leu476=	0,00196
	GLB1	Chr3:33058304	T>C		0,00393
	GLB1	Chr3:33058310	1370G>A	p.Arg457Gln	0,00393
	GLB1	Chr3:33058314	C>A		0,00589
	GLB1	Chr3:33059981	913C>T	p.Leu305Phe	0,00589
	GLB1	Chr3:rs34421970	T>C		0,00982
	GLB1	Chr3: 33063050	1233+8T>C		0,11198
	GLB1	Chr3:33093515	793-19C>T		0,00786
	GLB1	Chr3:33094973	792+10G>T		0,04912
	GLB1	Chr3:33106934	552+21G>A		0,00589
	GLB1	Chr3:33107060	458-11T>C		0,02947
	GLB1	Chr3:33109814	C>A		0,00196
	GLB1	Chr3:33110383	325C>T	p.Arg109Trp	0,01375
	GLB1	Chr3:33113992	T>G		0,01768
	GLB1	Chr3:33118597	G>T		0,00393
	GLB1	Chr3:33118631,	G>A		0,05894
	GLB1	Chr3:33118725	C>T		0,00393
	GLB1	Chr3:33134385	G>A		0,00982
	GLB1	Chr3:33134392	G>A		0,00589
	GLB1	Chr3:33134598	T>C		0,09430
	GLB1	Chr3:33134676	C>A		0,00786
	GLB1	Chr3:33134707	GTCC>G		0,00393

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	GLB1	Chr3:33134720	C>A		0,00982
	GLB1	Chr3:33135151	G>A		0,01179
MPS IV - Morquio A síndrome B	GLB1	Chr3:33135231	C>A		0,01572
	GLB1	Chr3:33135232	G>A		0,01179
	GLB1	Chr3:33138544	34T>C	p.Leu12=	0,35363
	GLB1	Chr3:33138614	c.-37C>G		0,27308
	ARSB	chr5:78076294	C>A		0,00393
	ARSB	chr5:78076460	1362G>A	p. Pro454=	0,02358
	ARSB	Chr5:78076517	G>C		0,10216
	ARSB	Chr5: 78077829	1214-32T>C		0,02358
	ARSB	Chr5: 78111892	T>A		0,00393
	ARSB	Chr5:78135201	1191G>A	p. Pro397=	0,09823
	ARSB	Chr5: 78135241	1151G>A	p.Ser384Asn	0,03143
	ARSB	Chr5:78135276	1143-27A>C		0,24558
	ARSB	Chr5: 78181423	1126G>A	p.Val376Met	0,13949
	ARSB	Chr5:78181477	1072G>A	p.Val358Met	0,19057
	ARSB	Chr5:78181481	1068A>T	p.Thr356=	0,00393
	ARSB	Chr5: 78181577	972A>G	p.Gly324=	0,01375
	ARSB	Chr5:78251347	691-22T>C		0,07073
MPS VI - Maroteaux-Lamy syndrome	ARSB	Chr5:78260406	A>G		0,00393
	ARSB	Chr5:78264879	A>G		0,00393
	ARSB	Chr5:78265041,	313-26T>C		0,19253
	ARSB	Chr5:78265051	C>A		0,00196
	ARSB	Chr5: 78280721,	C>A		0,00589
	ARSB	Chr5:78280731	G>A		0,00393
	ARSB	Chr5:78280741	C>A		0,00589
	ARSB	Chr5:78280751,	G>A		0,00393
	ARSB	Chr5:78280759	C>A		0,00196
	ARSB	Chr5:78280767	C>A		0,00196
	ARSB	Chr5:78280778	C>A		0,00393
	ARSB	Chr:78280943	C>A		0,00393
	ARSB	Chr:78280951	C>A		0,00196
	ARSB	Chr:78281112	C>A		0,00589
	GUSB	Chr5:21459730	G>T		0,00786
	GUSB	Chr5:21470675	C>A		0,01768
	GUSB	Chr5:21491446	G>T		0,25737
	GUSB	Chr5:21495221	A>C		0,00786
	GUSB	Chr5:21495250	G>C		0,01375
	GUSB	Chr5:21495276	C>T		0,01572
MPS VIII- Sly syndrome	GUSB	Chr5:21497180	G>A		0,01179
	GUSB	Chr5:21497187	C>T		0,01572
	GUSB	Chr5:21497216	T>C		0,00393
	GUSB	Chr5:68931069	G>C		0,11198
	GUSB	Chr5:68931122	C>A		0,07073
	GUSB	Chr5:68931132	G>A		0,03536
	GUSB	Chr5:68931140	A>G		0,09823

Table 1. Cont..

Type MPS	Gen	Position	nucleotide change	Amino acid change	Allelic frequency
	GUSB	Chr5:68931142	T>G		0,00393
	GUSB	Chr5:68931163	C>G		0,00393
	GUSB	Chr5:68931230	C>T		0,01965
	GUSB	Chr5:68931498	C>T		0,02554
	GUSB	Chr5:68931550	C>T		0,00786
	GUSB	Chr5:68931777	G>A		0,01572
	GUSB	Chr5:68931795	T>C		0,00982
	GUSB	Chr5:68931885	A>G		0,01179
	GUSB	Chr5:68931933	C>G		0,03340
	GUSB	Chr5:68932186	C>CTT		0,01965
	GUSB	Chr6:58250813	G>A		0,01375
	GUSB	Chr6:58250856	T>C		0,03143
	GUSB	Chr6:57245114	G>A		0,01572
	GUSB	Chr7: 57245137	T>C		0,00393
	GUSB	Chr7:57245156	G>A		0,00393
	GUSB	Chr7: 57245184	G>A		0,03536
	GUSB	Chr7:57245205	T>C		0,00393
	GUSB	Chr7:57245216	C>A		0,00393
MPS VIII- Sly syndrome	GUSB	Chr7:57245958	G>A		0,01179
	GUSB	Chr7:57247635	C>T		0,00393
	GUSB	Chr7:65425894	1946T>C	p.Leu649Pro	0,27505
	GUSB	Chr7:65426054	C>A		0,23772
	GUSB	Chr7:65429359	1740C>T	p.Tyr580=	0,09823
	GUSB	Chr7:65435401	C>A		0,00786
	GUSB	Chr7:65439344	G>A		0,00786
	GUSB	Chr7: 65439451	C>G		0,01179
	GUSB	Chr7:65439467	C>T		0,00786
	GUSB	Chr7:65439879	1065+27C>G		0,25933
	GUSB	Chr7:65441106	C>A		0,04322
	GUSB	Chr7:65444359	T>TGA		0,47151
	GUSB	Chr7:65445173	C>T		0,04322
	GUSB	Chr7:65445180	A>C		0,02750
	GUSB	Chr7:65445184	G>C		0,01572
	GUSB	Chr7:65445385	222C>T	p.Thr74=	0,01179
	GUSB	Chr7:65447004	C>A		0,01965
	GUSB	Chr7:65447009	162C>T	p.Asn54=	0,00786
	GUSB	Chr7: 65447182	c:-12G>A		0,06090
	HYAL1	Chr3:50334231	T>A		0,02358
	HYAL1	Chr3:50334359	T>C		0,05108
	HYAL1	Chr3:50336661	T>C		0,02554
	HYAL1	Chr3:50340154	C>A		0,03536
	HYAL1	Chr3:50334114	G>A		0,00589
MPS IX - Natowicz syndrome	HYAL1	Chr3:50339622	766G>A	Gly256Arg	0,02750
	HYAL1	Chr3:50332690	C>A		0,01572
	HYAL1	Chr3:50339564	G>T		0,00786
	HYAL1	Chr3:50339939	C>A		0,01375
	HYAL1	Chr3:50332697	G>A		0,00589
	HYAL1	Chr3:50334700	C>T		0,01179

transversion C>A (0.01375) and Chr8:42995811 C>T (0.04322). As for the 19 alleles reported in the GNS gene, the one with the highest frequency of appearance was the new report occurred in the position Chr12:65150485 C>T (0.30255); followed by the allele p.Pro66= with a frequency of 0.22593 and the change C>T occurred in the position Chr12:65141588 (0.09037).

Regarding those associated with MPS IV, 68 different alleles were reported for the GALNS gene, having the variants p.Glu477=, 634-19G>A, p.His236= frequencies of 0.22200, 0.15914, and 0.15717, respectively. Likewise, for the gene GLB1, 91 allelic variants were reported, of which the allele p.Leu12= was presented with the highest frequency (0.35363), followed by p.Arg521Cys (0.36149) and c.-37C>G (0.27308).

For the MPS VI associated ARSB gene, 27 allelic variants were tabulated. The intronic change 1143-27A>C showed higher frequency (0.24558), followed by 313-26T>C (0.19253) and p.Val358Met (0.19057).

Concerning the GUSB gene associated with MPSVIII, 50 allelic variants were found. The change located in Chr7:65444359, consistent with T>TGA showed the highest frequency among all the findings of the work, showing allele frequency values of 0.47151 with presence in 240/320 samples.

Finally, over the 11 allele variants found in the gene HYAL1, associated with MPS IX, it was reported that the change Chr3:50334359 T>C was the one that showed the highest frequency (0.05108) among all the variants of this gene, followed by Gly256Arg (0.02750).

Discussion

In recent years, with the advent of diagnostic techniques based on massive DNA sequencing, the increase of information regarding variants associated with different diseases has been made possible and facilitated. This technology has allowed the identification of thousands of alleles relate to the etiopathogenesis of a wide variety of diseases, as well as the recognition of biomarkers that could be used to inform disease prediction, identification of causal mechanisms, and the prioritization of new biological targets in drug discovery programs [11].

There are very few studies and with limited information on the calculation of allele frequency estimates of the variants of the MPS complex in the Colombian population, geographically delimited, with a reduced number of participants, and with technical methodological deficiencies, which leads to a partial and not adequate knowledge for its integrated approach that includes a family study and identification of carriers for the recognition of the risk of heritability.

For the present study of allele frequency carried out through the complete exome sequencing using the Illumina platform in 320 patients from South-Western Colombia without a clinical diagnosis of MPS, 509 variants associated with the MPS complex were reported. Among them, 262 had not been previously reported, which enhances the importance of their study, classification, effect in the functionality of the protein, and population expression.

The allele frequencies reported in these patients with diverse pathologies and not clinically diagnosed with MPS ranged from 0.00393 (2 alleles) to 0.47937 (248 alleles). Research conducted by Gomez *et al.* (2012) on patients affected by MPS, for MPS I and II, found 0.45 cases per 100,000 births for each of them. The frequency found for ¨MPS III in Cundinamarca and Boyacá, 0.17 cases per 100,000 live births. They did not find any patients with MPS type VII and IX [6].

The IDUA gene had the highest percentage of recognized alleles (24%), 11 of which were distributed between exons 1 and 10 and introns 5 and 7 and found in the study by Bertola *et al.* (2011) with patients confirmed with MPS I [12]. The heterogeneity and the prevalence of mutations highlight the importance of multinational screening studies to help elucidate the genotype-phenotype relationship in disorders such as MPS I that is characterized by extensive allelic heterogeneity.

As for the alleles, 14% of them were identified in the GALNS gene, characterized by being one of the most studied worldwide, with high mutational frequencies. In this study, the variant c.1431G>A was the most frequent with 60% of the alleles, followed in frequency by the benign mutations p.H36= and the intronic variant 634-19G>A with 41% and 34%, respectively. These alleles were not present in the population affected by MPS IVA, and for that, they are considered polymorphisms [13, 14].

In all the other genes associated with the MPS complex, there were not found alleles that show a high incidence in the affected population. For this reason, the current literature about the possible mutations associated with these genes is reduced, generating a relevant component in the knowledge of the polymorphisms found in people without the disease.

The frequency of the genetic variants varies by changing the allele frequencies. Thus, if there are two alleles in the same gene, it is polymorphic, and each new allele that emerges in the population increases the polymorphism of the gene. To be considered as such, the frequency of the most common allele must be less than 99%, and for a rare allele, it must exceed at least 0.005% of the frequency in the population; alleles that do not reach these frequencies are considered rare [15]. Genetic variants being aside from the scope of association studies with most statistical power is believed to contribute to a lack heritability of many human features, including common variants (denoted by a frequency of minor alleles [MAF]> 5%) of weak effect, low frequency (MAF 1-5%), and rare variants (MAF <1%) of small to moderate effect, or a combination of both with several possible scenarios, all considered plausible in simulation studies [16, 17].

In conclusion, despite finding a great diversity of alleles in the genes associated with mucopolysaccharidosis, the vast majority of these have been associated with benign phenotypes and are not reported in patients presenting the disease, so they could be could be polymorphisms in this population without the disease

Additional efforts to discover associations driven by rare and low-frequency variants through exome sequencing and

efforts in bioinformatics research allow continuous advances in the proportion of heritability explained by variants across the frequency spectrum. Heritability estimates for the entire genome depend, to a great extent, on assumptions about the imbalance of binding, frequency of the alleles, and genotype certainty. Therefore, future studies around these assumptions will be necessary to understand the impact of the alleles on the phenotype-genotype of patients.

Finally, studies based on allelic frequency estimates allow a better approach to the timely diagnosis and proper management of pathologies, since, by suggesting corresponding correlation tests of genotype and phenotypic indicators, to know the alleles present will allow to determine in a timelier manner the incidence and participation of many of these in the MPS complex.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The authors declare no conflict of interest.

References

1. Lin H-Y, Chan W-C, Chen L-J, *et al.* Ophthalmologic manifestations in Taiwanese patients with mucopo lysaccharidoses. *Mol Genet Genomic Med*. 2019;7(5):e00617. doi:10.1002/mgg3.617
2. Moreno-Giraldo LJ, Satizábal-Soto JM, Sanchéz-Gomez A. Genomic variability of the mucopolysaccharidosis complex in southwestern Colombia. *Genet Mol Res*. 2020;19(2):GMR18502. doi:10.4238/gmr18502
3. Manger B. Lysosomal storage diseases. *Z Rheumatol*. 2010;69(6):527-538. doi:10.1007/s00393–010–0627–z
4. Stapleton M, Hoshina H, Sawamoto K, *et al.* Critical review of current MPS guidelines and management. *Mol Genet Metab*. 2019;126(3):238-245. doi:10.1016/j.ymgme.2018.07.001
5. Khan SA, Peracha H, Ballhausen D, *et al.* Epidemiology of mucopolysaccharidoses. *Mol Genet Metab*. 2017;121(3):227-240. doi:10.1016/j.ymgme.2017.05.016
6. Gómez AM, García-Robles R, Suárez-Obando F. Estimación de las frecuencias de las mucopolisacaridosis y análisis de agrupamiento espacial en los departamentos de Cundinamarca y Boyacá. *Biomedica*. 2012;32(4):602-609. doi:10.1590/S0120–41572012000400015
7. Ministerio de Salud y Protección Social. Resolución número 005265 de 2018. Bogota(CO): Ministerio de Salud; 2018. http://www.acgh.com.co/publicaciones/149-reporte-enfermedades-huerfanas-raras-sivigila. Accessed 12 July 2019.
8. Instituto Nacional de Salud. Comportamiento epidemiológico de las enfermedades huérfanas. Colombia, 2016 hasta semana epidemiológica 05 de 2019. Bogota(CO): Instituto Nacional de Salud; 2019.
9. Barrera LA. Estudios Bioquímicos de los errores innatos del metabolismo en Colombia, durante dos décadas. *Rev Acad Colomb Cienc*. 2009;33:377-394.
10. Bernal JE, Briceno I. Genetic and other diseases in the pottery of Tumaco-La Tolita culture in Colombia-Ecuador. *Clin Genet*. 2006;70(3):188-191. doi:10.1111/j.1399–0004.2006.00670.x
11. Amorim CEG, Gao Z, Baker Z, *et al.* The population genetics of human disease: The case of recessive, lethal mutations. *PLoS Genet*. 2017;13(9):e1006915. doi: 10.1371/journal.pgen.1006915
12. Bertola F, Filocamo M, Casati G, *et al.* IDUA mutational profiling of a cohort of 102 European patients with mucopolysaccharidosis type I: identification and characterization of 35 novel α-L-iduronidase (IDUA) alleles. *Hum Mutat*. 2011;32(6):e2189-e2210. doi:10.1002/humu.21479
13. Cacioti A, Tonin R, Rigoldi M, *et al.* Optimizing the molecular diagnosis of GALNS: novel methods to define and characterize Morquio-A syndrome-associated mutations. *Hum Mutat*. 2015;36(3):357-368. doi:10.1002/humu.22751
14. Morrone A, Caciotti A, Atwood R, *et al.* Morquio a syndrome-associated mutations: A review of alterations in the GALNS gene and a new locus-specific database. *Hum Mutat.* 2014;35(11):1271-1279. doi: 10.1002/humu.22635
15. Hernández-Rodríguez AW, Trejo-Medinilla FM. Estudio genético poblacional de frecuencias alélicas para 15 marcadores STR presentes en la población del Estado de Zacatecas aplicado a la práctica forense. *Arch Med*. 2014;10(1):1. doi:10.3823/1209
16. Bomba L, Walter K, Soranzo N. The impact of rare and low-frequency genetic variants in common disease. *Genome Biol.* 2017;18(1):77. doi:10.1186/s13059–017–1212–4
17. Zanetti A, D'Avanzo F, Rigon L, *et al.* Molecular diagnosis of patients affected by mucopolysaccharidosis: A multicenter study. *Eur J Pediatr.* 2019;178(5):739-753. doi: 10.1007/s00431-019-03341-8