Acosta et al., J Genet Disor Genet Rep 2017, 6:1
DOI: 10.4172/2327-5790.1000151

Journal of Genetic Disorders & Genetic Reports

Case Report

A SCITECHNOL JOURNAL

Identification of a Novel Mutation in the Human *ARSB* Gene on Chromosome 5q14.1 for Autosomal Recessive Mucopolysaccharidosis Type VI Patients in Southwest Colombia

Acosta MA[1*], Lago RM[2], Barros F[2] and Carracedo AM[2,3]

Abstract

Mucopolysaccharidosis VI is a rare lysosomal storage hereditary disease, caused by arylsulfatase B enzyme deficiency which leads to the accumulation of harmful amounts of dermatan sulfate.

Methods: A total of 32 MPS VI patients were identified in Colombia, sixteen (45 %) in the Department of Cauca, identified clinically and by enzymatic assay. Two of these individuals belong to the Guambiano Amerindian reservation. DNA extraction and sequencing for the region of the arylsulfatase B by *ABI PRISM® 3100 Genetic Analyzer* was performed for these two index cases and 22 of their relatives. A principal component analysis of the genetic haplotypes was also performed.

Results: We found a novel single nucleotide change (p.Ser403X) in the *ARSB* gene, homozygous for the patient and heterozygous for their relatives, and classified as pathogenic. Cases and their relatives shared the same haplotype.

Conclusion: Together with the genealogy analysis, these results suggest a common ancestral allele in the Guambiano Amerindian reservation in the Department of Cauca and a novel mutation for MPS VI.

Keywords

Maroteaux-Lamy syndrome; Mucopolysaccharidosis VI; Novel mutation; Ancestral allel

Abbreviations: ARSB: Arylsulfatase B; cm: Centimeter; CP: Cephalic Perimeter; DIC: Intercanthal Distance; DIM: Internipple Distance; DNA: Deoxyribonucleic Acid; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; G2B2: 2 Gestations and 2Llife Births; GAGs: Glycosaminoglycan; HGVS: Human Genome Variation Society; Kg: Kilogram; MPS: Mucopolysaccharidosis; MPS IV: Mucopolysaccharidosis VI; mol/h: Mole/hour; PEF: Peak Expiratory Flow; SNPs: Single Nucleotide Polymorphisms; SS/SI: Superior Segment /Inferior Segment; TP: Thoracic Perimeter; µg/mg: Micrograms/miligram

***Corresponding author:** Acosta MA, PhD, Pediatrics Department, Facultad de Medicina, Universidad del Cauca, Carrera 6 No. 13N-50 Popayán-Cauca, Colombia, Tel: 573175282523; Fax: 5728230262; E-mail: morin1924@gmail.com

Received: January 25, 2017 **Accepted:** February 18, 2017 **Published:** February 25, 2017

Introduction

Mucopolysaccharidosis type VI (MPS VI) or Maroteaux-Lamy syndrome is a rare and severe autosomal recessive disease in humans caused by impaired activity of the lysosomal enzyme hydrolase N-acetylgalactosamine 4-sulfatase or arylsulfatase B [1], resulting from mutations in the *ARSB* gene (OMIM # 253200) [2]. The enzyme deficiency leads to the accumulation of harmful amounts of ungraded dermatan sulfate inside the lysosomes, causing progressive damage of several tissues. Patients present with a wide clinical spectrum (clinical heterogeneity), ranging from severe to mild forms of disease progression [3]. Severity correlates with the age of onset, organ involvement and disease progression [3-5]. The severe phenotype exhibits a rapidly progressing MPS VI characterized by early onset of symptoms and short life expectancy (20-30 years) [6]; this correlates with certain alleles and urinary glycosaminoglycan (GAGs) levels higher than 100 µg / mg. On the other hand, the mild form is associated with delayed onset of signs and symptoms, and levels of GAGs less than 100 µg / mg [4].

The *ARSB* gene, located on the long arm of chromosome 5 (5q13.3-q14.1) [7], consists of 8 exons spanning less than 440 kb and encoding for a 533-aminoacid polypeptide and a 37-aminoacid signaling peptide [8]. Translocation across the endoplasmic reticulum membrane occurs through cleavage of the signaling peptide and glycosylation of asparagine residues [7]. The *ARSB* gene has 3910 intragenic Single Nucleotide Polymorphisms (SNPs), and 68 regulatory elements such as promoters, enhancers and binding sites for transcription factors [9].

Like other mucopolysaccharidosis, MPS VI can be caused by different types of mutations in the *ARSB* gene such as deletions, insertions, missense, nonsense, as well as mutations in splicing sites (Figure 1).

Such mutations have been identified in patients from North and South America, Europe, Australia and Asia, with clear genotype-phenotype correlations in some cases. The most common mutations identified in patients from North America, South America, Europe and Australasia are c.629A>G, c.944G>A, c.1143-8T>G, c.1143-1G>C and c.1151G>A [10] with a frequency higher than 10 %. Most of these mutations are produced by single nucleotide changes, which lead to loss of transcription. The prevalence of these mutations is mainly reported in Russia, Australia, USA, France, Germany, Portugal, Italy, China, Brazil, Colombia, Chile, Argentina and Spain [1,4,11-21]. New mutations are reported on a regular basis [22,23] and attempts are being made to establish the corresponding phenotype-genotype correlations.

To date, 139 mutations in the *ARSB* gene have been identified, according to entries in the Human Gene Mutation Data Base and recent publications (Figure 1) [10].

Materials and Methods

A total of 36 MPS VI patients were identified in Colombia, 16 of them (45 %) in the Department of Cauca. Of these 16 patients who were fully classified according to their clinical and enzymatic assay profile (results not available), two belong to a Guambiano Amerindian reservation (municipality of Silvia) (Figure 2).

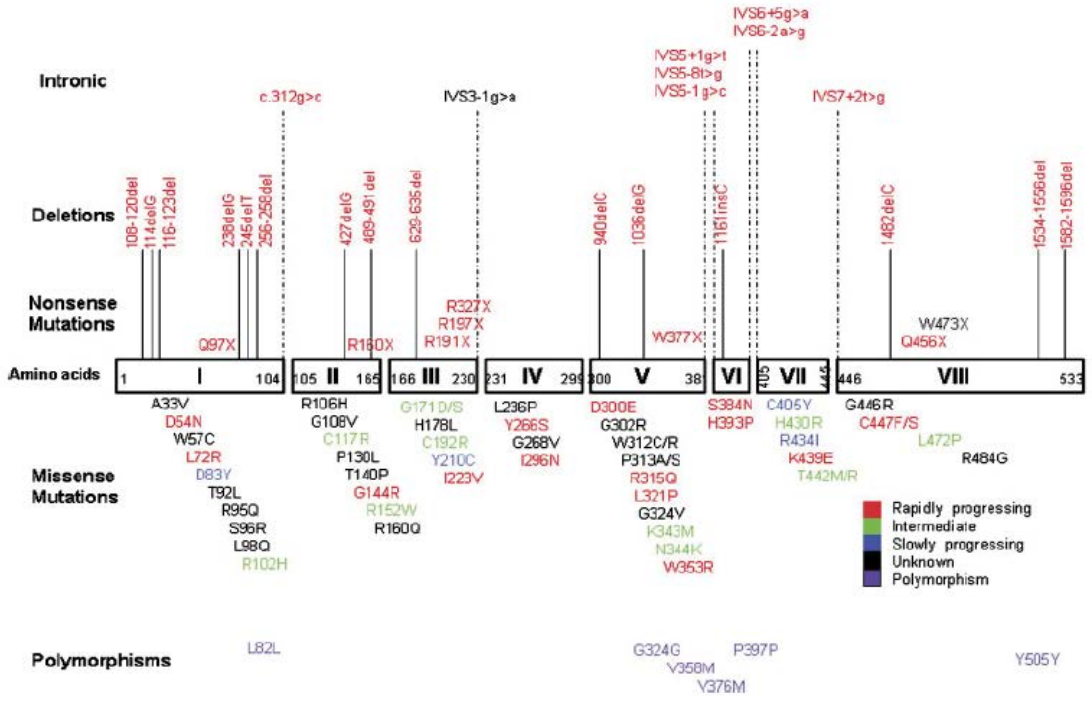


Figure 1: *ARSB* mutations according to their location within the gene. The exons are represented as rectangles and numbered with Roman numerals. Prediction of the severity is shown in color according to the legend [19].

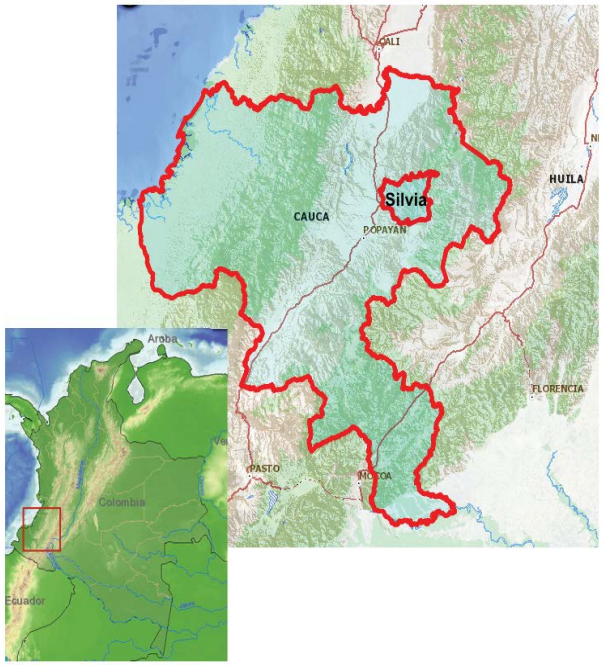


Figure 2: Municipality of Silvia (Department of Cauca - Southwest Colombia).

Taken from: Instituto de Cartografía Agustín Codazzi. 2016. "Mapa De Cartografía Básica." *Geoportal*. Accessed July 19. http://www.igac.gov.co/wps/portal/igac/raiz/iniciohome/.

These two patients were reported as index cases and, together with their 22 relatives (from 2 different families), were put through the following protocol: DNA extraction, amplification, purification and sequencing reaction for the genomic DNA of arylsulfatase B in a capillary electrophoresis instrument *ABI PRISM® 3100 Genetic Analyzer*. The results of genomic DNA were placed in the format and reading sequence alignment required for the "*staden package*" [24]. The intragroup and sequence differences were determined by comparison to the reference genome sequence encoding for arylsulfatase B [8]. In addition, a complete and comprehensive analysis of the *ARSB* gene by sequencing analysis of the 8 exons with the flanking intron-exon was performed.

The main component analysis of the genetic haplotypes was done using the method for SNPs genotyping based on the *Sequenom MassARRAY platform* [25] and the *Haploview software* [26].

Results

Clinical phenotype of index cases

F1 index case: A 4-year old male patient coming from the Cacique Alto village in the Guambiano-Cauca reservation, born to a 22-year old woman G2B2 who reported occasional exposure to pesticide sprays during pregnancy, positive fetal movements, cephalic presentation and home birth. Both parents are of indigenous origin. The family history includes treated pulmonary tuberculosis in the maternal grandmother, a speech disorder in a maternal aunt, and three individuals of the same family who died young with a similar undiagnosed clinical picture (Guambiano family F1, Figure 3).

The patient initially presented a giant umbilical hernia, progressive corneal opacity, dorsolumbar spine deformity (Figure 4.2) and

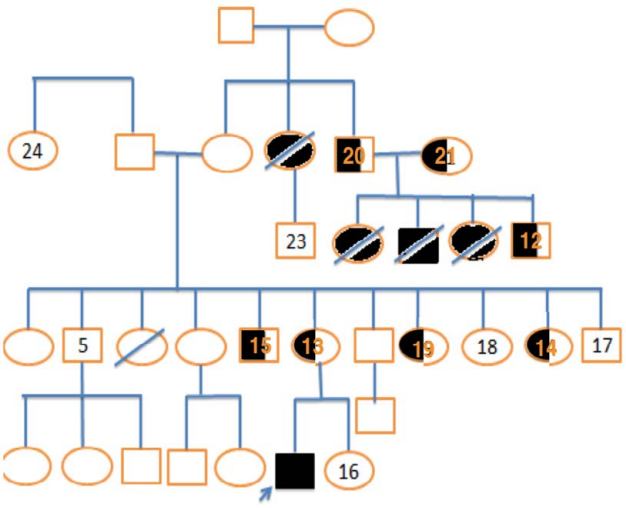


Figure 3: F1 Family Pedigree showing four affected individuals and the index case; the 4 affected individuals died at an early age.

delayed motor development. The findings on physical examination were: weight: 12 kg, height: 89 cm, width: 81 cm, CP: 50 cm, TP: 53.5 cm, ICD: 80 × 30 mm, right pinna: 4.9 × 2.9 cm, left pinna: 4.8 × 2.9 cm, IND: 12.5 cm, SS/IS: 1.4, brachycephalic skull, pointed anterior fontanelle, thick hair with low hairline and prominent forehead, hirsutism, normal set ears, diffuse corneal opacity predominantly in the left eye, normal eye fundus, thick eyebrows, mongoloid palpebral fissures, broad depressed nasal dorsum, rough facies (Figure 4.1), thick lips, tendency to macroglossia, hypertrophic gums, poor quality dental enamel, short broad neck, increased bell-shaped anteroposterior thoracic diameter, horizontal ribs, systolic mitral focus murmur grade II/IV and pansystolic murmur, giant umbilical hernia, hepatomegaly ± 2 cm from the right costal margin, testes in the scrotum, normal anus, overall limb shortening with flexion contractures of the elbows (Figure 4.3), lumbosacral mongolian spot (Figure 4.2) and generalized hypertrichosis.

The audiogram revealed severe mixed, predominantly conductive hearing loss in the right ear and mild sensory hearing loss of the left ear. Radiographic assessments of the cranium showed increased anteroposterior and sellar diameters with "J" deformity; prominent Pachoni granulations, craniofacial disproportion and brachycephaly, deviated bony nasal septum and turbinate hypertrophy with reduced bilateral nasal patency. The cervico-dorso-lumbo-sacral spine radiograph showed increased interpeduncular distance of the vertebral bodies, notorious in particular in the lumbar segment; kyphosis of the dorsolumbar junction, L2 retrolisthesis, beak deformity of the lower T12, L1 and L2 angles (Figure 5.1). The radiograph of the rib cage showed bilateral costal spatula deformity (Figure 5.2). The pelvic radiograph showed bilateral coxofemoral subluxation, prominent sciatic spines and generalized osteopenia.

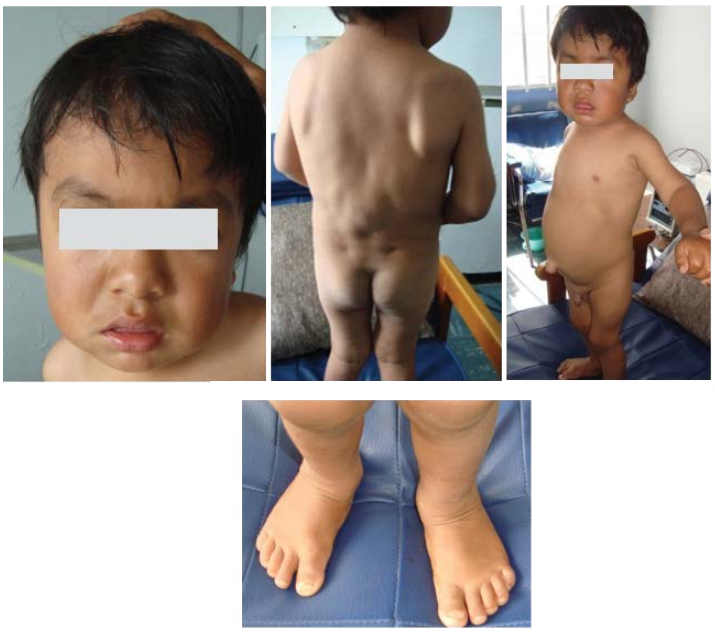
Comparative radiological examination of the upper limbs showed widening of the medullary region of the long bones with cortical thinning, bilateral inferior radio-ulnar diastasis, Madelung's deformity, metacarpal deformity with proximal metaphyseal thinning, delayed skeletal maturation and phalangeal widening (Figure 6.1). Comparative lower limb films show widening of the medullary regions with cortical thinning, hallux valgus and bilateral varus metatarsal bone (varus 2nd to 5th metatarsals) (Figure 6.2).

Echocardiography showed a dysmorphic mitral valve with mild stenosis and regurgitation, grade II prolapse of the anterior mitral valve, mild aortic stenosis and regurgitation, mild subaortic hypertrophy without a gradient. Spirometry showed a flow/volume curve with diminished FEV1, FVC and PEF (obstructive and restrictive abnormality) with no improvement with inhaled B2. Polysomnography revealed a mixed apnea pattern. Plain computed axial tomography of the abdomen revealed moderate hepatomegaly and increased pancreatic size, with no additional abnormalities. Cerebral magnetic resonance imaging showed an empty sella syndrome and spinal canal stenosis at the craniocervical junction due to soft tissue thickening posterior to the odontoid process and bilateral inflammatory changes of paranasal and mastoid sinuses. Spinal magnetic resonance imaging showed cervical stenosis with soft tissue involvement of C1-C2 posterior to the odontoid process, with dorsal deformity due to diminished anterior height, and reduced height of the anterior and posterior thirds.

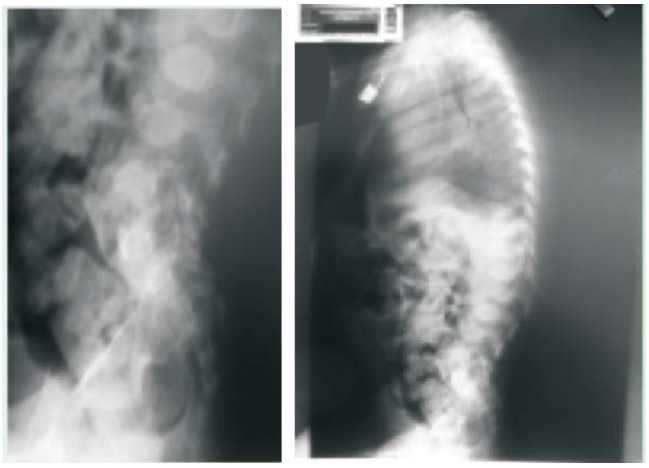
A clinical diagnosis of mucopolysaccharidosis type VI was made on the basis of these findings, while enzymatic activity filter-paper testing for arylsulfatase B showed a value of 2.1 µmol/h (reference value: >5 µmol/h), which was confirmed with a second filter paper sample, and leukocyte testing showed a value of 1.65 µmol/h (reference value: 5.31-21.85 µmol/h). Electrophoresis for MPS showed migration patterns corresponding to dermatan and chondroitin sulfate with positive quantification of urinary GAGs. This confirmed the clinical diagnosis, and enzyme replacement therapy was initiated in 2013.

F2 index case: A 5-year old female patient, first-born to a mother of 25 and a father of 26, both from the same indigenous reservation (Guambiano Family 2) (Figure 7).

The initial symptoms appeared at six months of age, with organomegaly, hearing loss, umbilical hernia and heart disease. At 10 months of age, the child developed congestive heart failure, secondary to patent ductus arteriosus, with hemodynamic repercussions, severe mitral regurgitation, tricuspid regurgitation and biventricular dysfunction. This required mitral valve replacement with a biological valve plus surgical closure of the patent ductus arteriosus. A presumptive diagnosis of MPS VI was made at 2 years of age and



Figures 4.1, 4.2, 4.3, 4.4: Images showing the clinical characteristics of patient F1 (short stature, rough facies, short neck, dysostosis multiplex, long philium, kyphosis and thoraco-lumbar hump, hirsutism and brachydactily).



Figures 5.1, 5.2: Chest and spinal X-rays of patient F1 showing beak deformity of the lumbar vertebral bodies in the middle third and L5 on S1 listhesis.

qualitative acid albumin and azure strip tests were positive. The result of the filter paper test for *ARSB* enzymatic activity was 2.9 µmol/h (reference value > 5 µmol/h), and it was confirmed by the result of a second filter paper test of 1.2 nmol/h/ml (reference value: 5.3-22 nmol/h/ml). The result for leukocyte arylsulfatase B was 30.38 nmol/mg protein/H (normal range: 115-226), confirming the diagnosis of MPS VI.

The physical examination showed evidence of disproportionate dwarfism, rough facies (Figure 8.1), corneal opacity, macroglossia, short neck, hepatomegaly 4 cm below the right costal margin, umbilical hernia (Figure 8.1), severe delayed psychomotor development, and dysostosis multiplex (Figure 8.2).

A computed axial tomography brain scan taken at 18 months of age showed ventricular dilatation (Figure 9). The echocardiogram showed a normally functioning biological valve, adequate biventricular function and mild left ventricular dilatation. Auditory evoked potentials showed profound neurological compromise of the right ear and profound to severe compromise of the left ear. Polysomnography showed desaturation of up to 79 %, possibly consistent with increased upper airway resistance.

Radiographic assessment showed increased anteroposterior skull diameter with a "J" sellar deformity, dorsolumbar kyphosis, left lumbar scoliosis, lumbarization of the first sacral vertebra, increased interpedicular distance in the dorsolumbar vertebrae, beak deformity of the inferior angle of the vertebral bodies of L2 and L3, with L2 retrolisthesis. The rib cage shows spatula costal deformity.

Films of the upper and lower limbs show widening of the medullary regions with cortical thinning and generalized osteopenia. There is delayed bone maturation, based on carpal bone ossification. In the pelvis, there is bilateral acetabular dysplasia with coxofemoral subluxation. At the the gait laboratory, the patient evidenced reduced hip mobility on the sagittal and coronal planes, with bilateral flexion deformity; knee flexion deformity; flat, valgus feet, and high-riding fibular malleoli; crouch gait pattern with very diminished gait speed due to short stride length, as well as signs of adenoid hypertrophy in the pharyngeal cavum with a 90 % reduction of the anteroposterior diameter of the rhinopharinx.

Molecular test results

After applying the previously described protocol, we found a single nucleotide change (p.S403X) in the *ARSB* gene of the two index cases (homozygous) (Figure 11) and 10 of their relatives (heterozygous) (Figure 11, Table 1).

According to the ALAMUT program, version 2 [27], this change found in exon 6 is a transversion that produces a nonsense mutation,

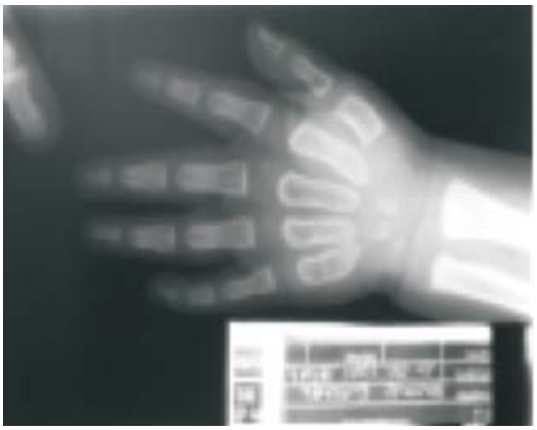


Figure 6.1: Hand radiograph showing wide irregular bones. Second and fifth metacarpals deformity of the with posterior beak.

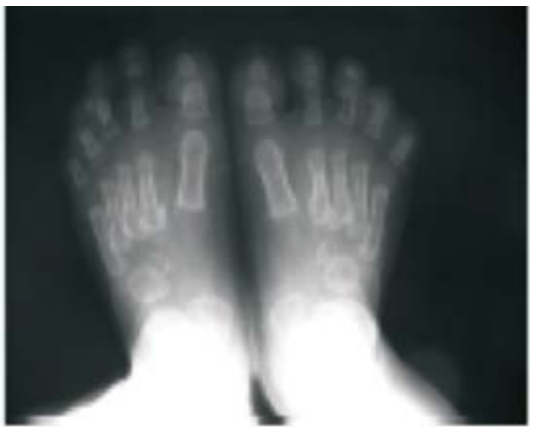


Figure 6.2: Radiograph of the feet showing bilateral talus varus with bilateral beak deformity of the posterior third of the second and third metatarsals.

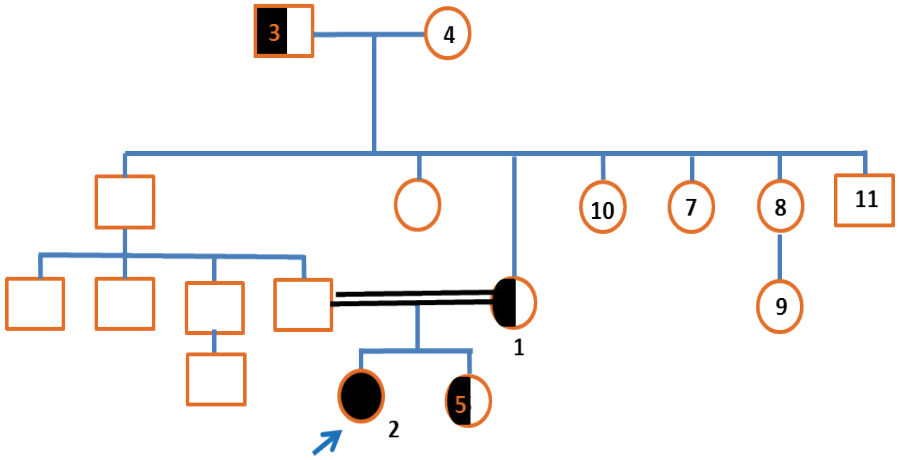
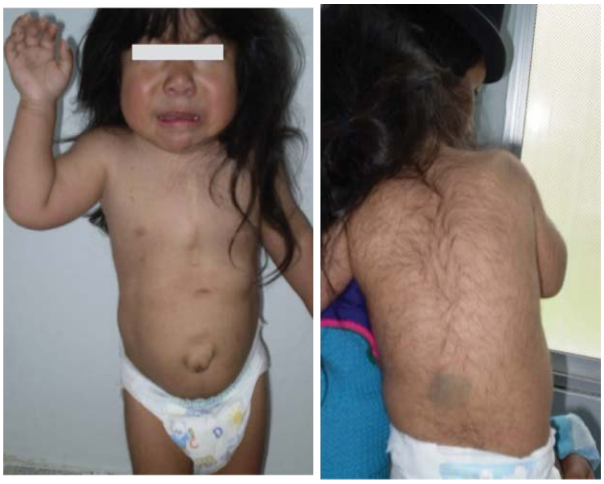


Figure 7: F2 Family Pedigree, showing a single index case (case 2) (Program Gen Pro).



Figures 8.1 and 8.2: Photographs showing the clinical characteristics of patient F2 (short height, rough facies, dysostosis multiplex, umbilical hernia, hypertrichosis, brachydactily and dorsal kyphosis). Images obtained with the parent's prior informed consent.

causing a premature stop codon. Following the recommendations of the HGVS program, version 2, this mutation will have the following nomenclature:

DNA Level (c DNA): NM_000046.3:c.1208C>A

DNA Level (genomic): Chr5(GRCh37):g.78135184G>T

Protein Level: p.Ser403X

Pos. 147327 (A/A) TCA>TAA

Mutation: Ser403Term

Guambiano families were studied with 62 SNPs, and a main component analysis of the genetic haplotypes was done using the method for SNPs genotyping based on the *Sequenom MassARRAY platform* [25], and the *Haploview software* [26]. The same haplotype (TTAATTT) was found in the probands and their relatives (Figure 12).

Discussion

The reported incidence of MPS VI ranges from 1 in 43,261 live births in Turkey to 1 in 1,505,160 live births in Sweden [28]. To date, there is no reported incidence of MPS VI in Colombia. Nevertheless,

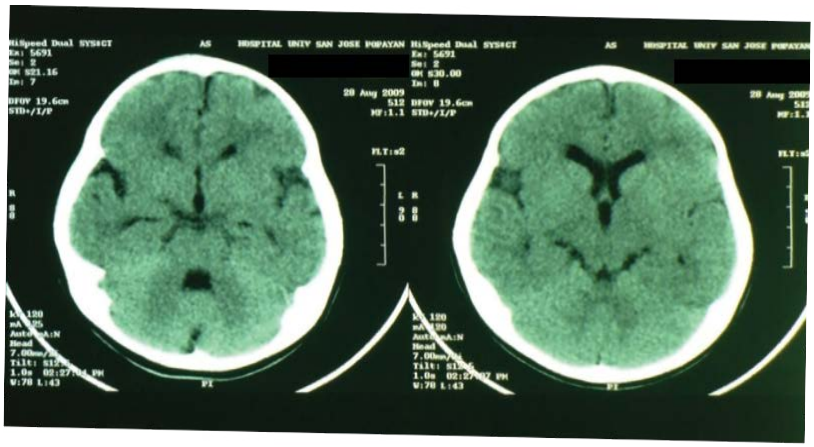
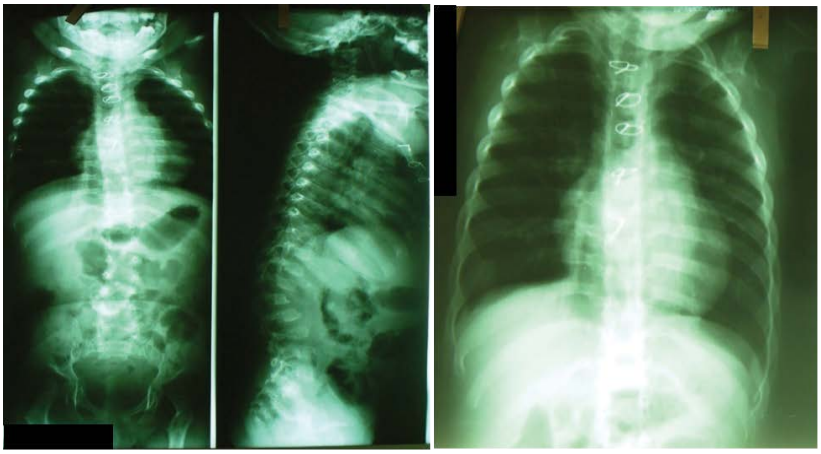


Figure 9: CT scan of the patient showing ventricular dilatation.



Figures 10.1 and 10.2: Chest X-ray showing moderate ventricular dilatation; radiograph showing moderate lumbar vertebral deformity.

a total of 36 cases have been identified nationwide, of which 16 come from the Southwest, an area of Colombia with Native American ethnicity.

This study reports a novel c.1208C>A mutation in the gene encoding for *ARSB* in two probands with MPS IV (homozygous) from the Guambiano population (Southwestern Colombia) and 10 carriers (heterozygous) within their families. High inbreeding in this population supports the clinical finding in the reservation, where there is a high frequency of genetic diseases, including MPS VI. This nonsense mutation is caused by a second base C>A substitution of a TCA codon encoding for serine in exon 6, leading to a TAA codon or stop codon (p.S403X). This results in a loss of the last 130 amino acids in the C-terminal end of the protein, which changes from a 533-aminoacid protein to a 402-aminoacid protein (Figure 13).

This shortening of the protein involves almost a complete loss of the lower domain of the enzyme, but leaves unchanged the main domain of the peptide sequence. Therefore, and based on the stability and preservation of the structure observed from that domain in different sulfatases, the three-dimensional structure of the truncated proteins would be expected to be very similar to the wild type in which the peptide fragment corresponding to the lower domain is deleted. This aberrant protein with its main domain preserved would have a 20-amino acid peptide chain in its C-terminal end, and most likely an absence of a secondary structure due to its short size, with an aberrant dissolution and crystalline state. The capacity of the protein to act as a sulfatase enzyme should remain unchanged by the p.S403X mutation, since the domain responsible for the catalytic process is intact. The biological function of the terminal domain remains unclear after the review of the literature [29,30]. However, according to the biological process in which the enzyme is involved, we think this domain is responsible for the molecular recognition of the substrate to be hydrolyzed, and for its solubility and bioavailability in the cell organelles and in the intracellular space.

The nonsense mutation and, therefore, the resulting truncated protein, will result in a higher exposure of the active domain to the intracellular space and, consequently, a considerable loss of selectivity against substrates. Additionally, the protein's solubility would change leading to a different bioavailability when compared to the wild type.

The clinical phenotype in the two homozygous index cases is explained by the impaired protein function previously described. Since MPS VI is an autosomal recessive disease, when both parents carry the heterozygous mutation, the offspring has a 25 % risk of having the disease. Our family study identified both mothers as carriers and multiple family members as carriers also. The two index cases displayed the classical phenotype for severe MPS VI and are currently under enzyme replacement therapy.

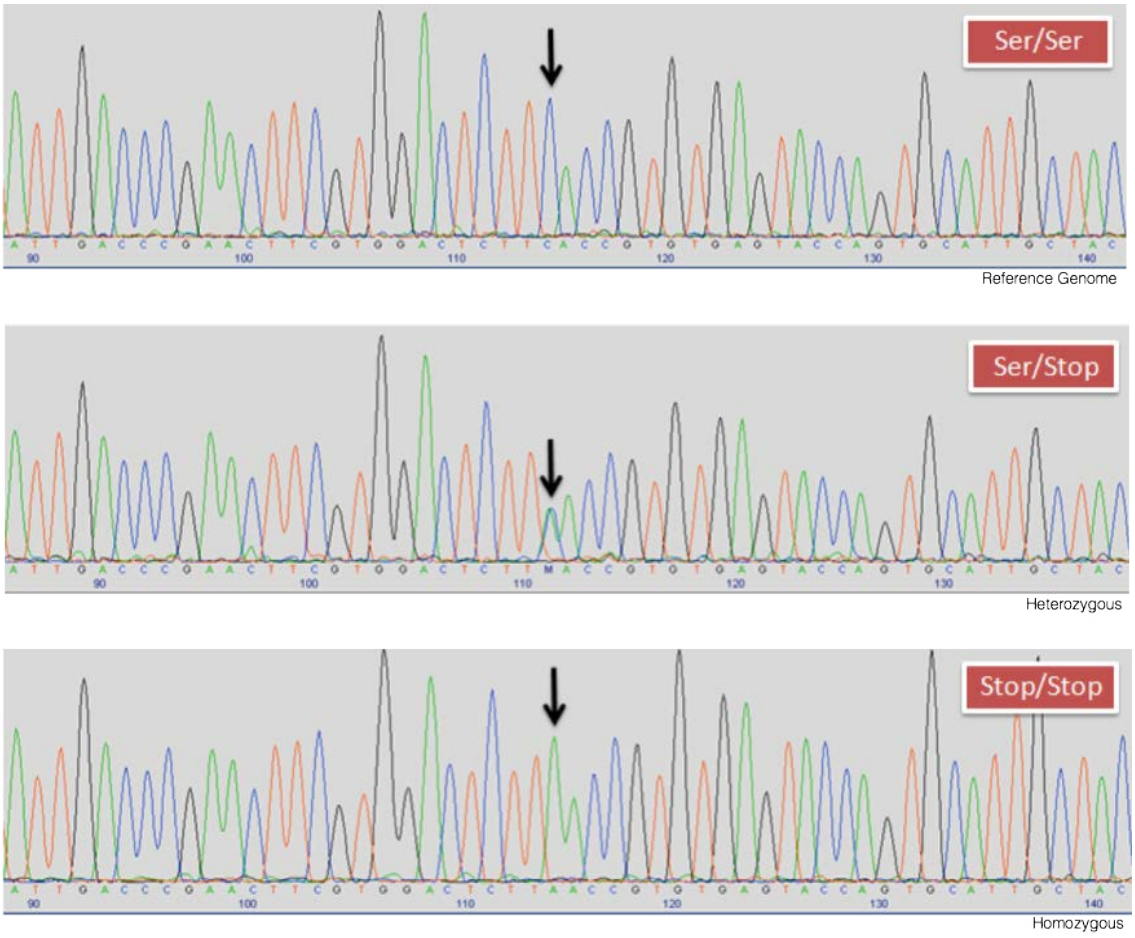


Figure 11: Electropherograms comparing the reference genome with a heterozygous relative and the homozygous proband (novel mutation: c.1208 C>A, p.S403X)

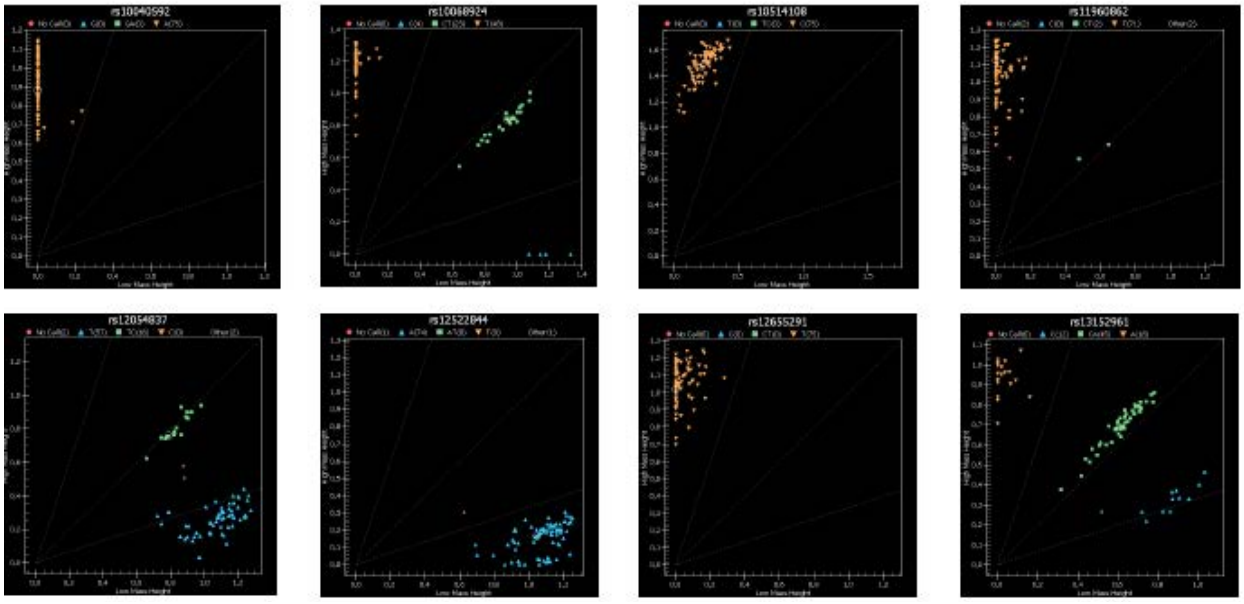


Figure 12: Genotyping with *Sequenom MassARRAY*.

Table 1: Mutation analysis for MPS VI probands and their relatives.

Patient #	dbSNP	cDNA	Protein	Site of mutation	Type of Mutation	Phenotype
1		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
2	Pos. 101034 (A/A) (rs1065757)	Pos. 147327 (A/A) TCA>TAA	S403X*	Exon 6	Nonsense	Homocygous
3		c.1208C>A	S403X*		Nonsense	Heterocygous
5		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
6	Pos. 101034 (A/A) (rs1065757)	Pos. 147321 (A/A) TCA>TAA	S403X*	Exon 6	Nonsense	Homocygous
12		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
13		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
14		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
15		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
19		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
20		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous
21		c.1208C>A	S403X*	Exon 6	Nonsense	Heterocygous

(*) Novel Mutation
Patients 4, 7-11, 16-18 and 22-24 didn´t present any genomic change
Cases 2 and 6 are index cases

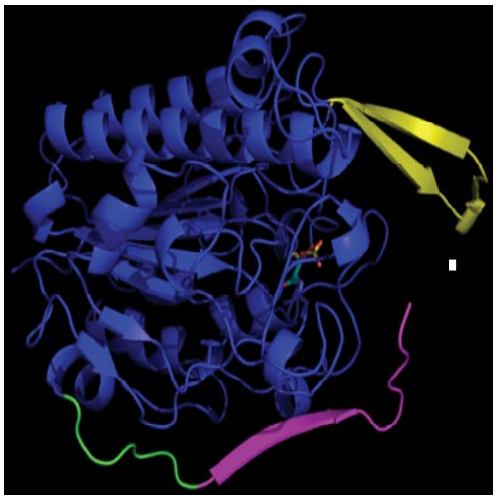


Figure 13: Theoretical structure proposed for sulfatase B truncated at amino acid 402.

(Author: José Manuel Otero Casas, Ph.D., Centro de Investigación en Química Biolóxica y Materiais Moleculares (CIQUS), Santiago de Compostela University, Spain).

Haplotype analysis using intragenic polymorphism analysis was able to probe a common ancestral allele for c.1208C >A in the population of the Guambiano reservation analyzed. The high inbreeding observed among the people of the Guambiano reservation contributed to the development of genetic diseases and of MPS VI in our case. This supports the hypothesis of a common ancestral allele.

Conclusions

Together with the genealogy analysis, these results suggest a common ancestral allele in the Guambiano Amerindian reservation in the Department of Cauca and point to a novel mutation for MPS VI.

Public health policies for the Southwestern region of Colombia must be oriented to health education through genetic counselling, including prevention of new cases in affected families and early diagnosis in the community, by means of neonatal metabolic screening programs and proper management of newly diagnosed cases.

Informed Consent

Informed consent has been obtained from the patients, parents and relatives.

Acknowledgments

We would like to thank the patients and their families for their kind cooperation. We would also like to thank José Manuel Otero Casas, Ph.D., and Centro de Investigación en Química Biolóxica y Materiais Moleculares (CIQUS), Santiago de Compostela University (Spain), for their support in the analysis of biochemical structural changes.

Declaration of Conflicting Interests

The authors declare not having any conflicts of interest.

Funding

This work was supported by Fundación Pública Galega de Medicina Xenómica and by Biomarin Colombia.

References

1. Garrido E, Cormand B, Hopwood JJ, Chabás A, Grinberg D, et al. (2008) Maroteaux–Lamy syndrome: Functional characterization of pathogenic mutations and polymorphisms in the arylsulfatase B gene. Mol Genet Metab 94: 305-312.
2. Online Mendelian Inheritance in Man, OMIM (TM) MIM Number: 253200.
3. Valayannopoulos V, Nicely H, Harmatz P, Turbeville S (2010) Mucopolysaccharidosis VI. Orphanet J Rare Dis 5: 5-20.
4. Litjens T, Hopwood JJ (2001) Mucopolysaccharidosis type VI: Structural and clinical implications of mutations in N-acetylgalactosamine-4-sulfatase. Hum Mutat 18: 282-295.
5. Vairo F, Federhen A, Baldo G, Riegel M, Burin M, et al. (2015) Diagnostic and treatment strategies in mucopolysaccharidosis VI. Appl Clin Genet 8: 245-255.
6. Giugliani R, Federhen A, Rojas MVM, Vieira T, Artigalás O, et al. (2010) Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. Genet Mol Biol 33: 589-604.
7. Litjens T, Baker EG, Beckmann KR, Morris CP, Hopwood JJ, et al. (1989) Chromosomal localization of ARSB, the gene for human N-acetylgalactosamine-4-sulphatase. Hum Genet 82: 67-68.
8. Aken BL, Ayling S, Barrell D, Clarke L, Curwen V, et al. (2016) The Ensembl gene annotation system. Database Gene: ARSB ENSG00000113273 [Internet]. Jun 23 2016.
9. Stenson PD, Mort M, Ball EV, Howells K, Phillips AD, et al. (2009) The Human Gene Mutation Database: 2008 update. Genome Med 1: 13.

10. Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, et al. (2003) Human Gene Mutation Database (HGMD®): 2003 update. Hum Mutat 21: 577-581.

11. Isbrandt D, Arlt G, Brooks DA, Hopwood JJ, Figura von K, et al. (1994) Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): Six unique arylsulfatase B gene alleles causing variable disease phenotypes. Am J Hum Genet 54: 454-463.

12. Voskoboeva E, Isbrandt D, Figura von K, Krasnopolskaya X, Peters C (1994) Four novel mutant alleles of the arylsulfatase B gene in two patients with intermediate form of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). Hum Genet 93: 259-264.

13. Litjens T, Morris CP, Robertson EF, Peters C, Figura von K, et al. (1992) An N-acetylgalactosamine-4-sulfatase mutation (ΔG238) results in a severe Maroteaux-Lamy phenotype. Hum Mutat 1: 397-402.

14. Bradford TM, Litjens T, Parkinson EJ, Hopwood JJ, Brooks DA (2002) Mucopolysaccharidosis Type VI (Maroteaux-Lamy Syndrome): A Y210C mutation causes either altered protein handling or altered protein function of N-Acetylgalactosamine 4-Sulfatase at multiple points in the vacuolar network. Biochemistry 41: 4962-4971.

15. Litjens T, Brooks DA, Peters C, Gibson GJ, Hopwood JJ (1996) Identification, expression, and biochemical characterization of N-acetylgalactosamine-4-sulfatase mutations and relationship with clinical phenotype in MPS-VI patients. Am J Hum Genet 58: 1127-1134.

16. Petry MFG, Dieter T, Burin M, Giugliani R, Leistner S (2003) Identification of a novel mutation in the ARSB gene that is frequent among Brazilian MPSVI patients. Genet Test 7: 347-349.

17. Garrido E, Chabás A, Coll MJ, Blanco M, Domínguez C, et al. (2007) Identification of the molecular defects in Spanish and Argentinian mucopolysaccharidosis VI (Maroteaux–Lamy syndrome) patients, including 9 novel mutations. Mol Genet Metab 92: 122-130.

18. Saito S, Ohno K, Sugawara K, Sakuraba H (2008) Structural and clinical implications of amino acid substitutions in N-acetylgalactosamine-4-sulfatase: Insight into mucopolysaccharidosis type VI. Mol Genet Meta 93: 419-425.

19. Karageorgos L, Brooks DA, Harmatz P, Ketteridge D, Pollard A, et al. (2007) Mutational analysis of mucopolysaccharidosis type VI patients undergoing a phase II trial of enzyme replacement therapy. Mol Genet Metab 90: 164-170.

20. Villani G, Balzano N, Di Natale P (1998) Two novel mutations of the arylsulfatase B gene in two Italian patients with severe form of mucopolysaccharidosis. Hum Mutat 11: 410.

21. Saito S, Ohno K, Sekijima M, Suzuki T, Sakuraba H (2012) Database of the clinical phenotypes, genotypes and mutant arylsulfatase B structures in mucopolysaccharidosis type VI. J Hum Genet 57: 280-282.

22. Kantaputra PN, Kayserili H, Guven Y, Kantaputra W, Balci MC, et al. (2014) Clinical manifestations of 17 patients affected with mucopolysaccharidosis type VI and eight novel ARSB mutations. Am J Med Genet 164: 1443-1453.

23. Giraldo GA, Ayala-Ramírez P, Prieto JC, García-Robles R, Acosta JC (2016) Molecular findings of Colombian patients with type VI mucopolysaccharidosis (Maroteaux–Lamy syndrome). Meta Gene 7: 83-89.

24. Staden R, Beal FK, Bonfield KJ (1998) The Standen Package. Methods Mol Biol 132: 115-130.

25. Gabriel S, Ziaugra L, Tabbaa D (2009) SNP Genotyping Using the Sequenom MassARRAY iPLEX Platform. In: Current Protocols in Human Genetics. John Wiley & Sons, New Jersey, pp: 190-196.

26. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: Analysis and visualization of LD and haplotype maps. Bioinformatics 21: 263-265.

27. Alamut Visual version. Interactive Biosoftware. Rouen, France.

28. Lin WD, Lin SP, Wang CH, Hwu WL, Chuang CK, et al. (2008) Genetic analysis of mucopolysaccharidosis type VI in Taiwanese patients. Clin Chim Act 394: 89-93.

29. GeneCards: Encyclopedia for genes, proteins and diseases: ARSB Gene.

30. Human Protein Atlas: ARSB Gene.

Author Affiliation

Top

[1]*Paediatrics Department, Cauca University School of Medicine, Popayán (Colombia): Carrera 6 No. 13N-50, Colombia*

[2]*Clinical Hospital of Santiago de Compostela, Galicia, Spain: Rúa San Francisco s/n 15782, Spain*

[3]*Pathology Department, University of Santiago de Compostela School of Medicine, Galicia, Spain: Rúa San Francisco s/n 15782, Spain*