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Same Mutation in Two Patients of Southwestern Colombia with Mucopolysaccharidosis Type VI or Maroteaux-Lamy Syndrome: Is there an Endogamic Effect?

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ABSTRACT

Mucopolysaccharidosis type VI, is a rare genetic disease caused by a deficiency of the N-acetylgalactosamine-4-sulfatase enzyme, also known as aryl sulfatase B. In Colombia, there are 36 known cases, of which 10 are in an indigenous group with an estimated prevalence of 1/1,140,000. New mutations are published continuously and, to date, 140 have been reported. The main objective of this study is to characterize, by molecular genetics, two patients identified in Southwestern Colombia (Department of Cauca) with the severe form of MPS type VI. A single nucleotide (p.C447F) pathogenic transversion producing a sense change mutation was found in the two index cases on exon 8 of the *ARSB* gene. This gives rise to the exchange of one amino acid for another on the minor domain of the enzyme: position 206,029 (T/T) TGT>TTT. An unusual frequency of genetic diseases is found in the department of Cauca in Colombia. In this study, the two index patients exhibit the same mutation, suggesting the possibility of a common ancestral allele, probably due to the relative inbreeding and the geographical isolation of these regions. The above highlights the importance of public health policies in our country, genetic counseling, neonatal screening and identification of new cases in areas where incidence is above average.

Keywords: Lysosomal diseases, Muco polysaccharidosis type VI, Matoreaux-Lamy syndrome

INTRODUCTION

Mucopolysaccharidosis type VI (MPS VI) or Maroteaux–Lamy syndrome (OMIM #253200), is a rare genetic disease caused by a deficiency of the N-acetylgalactosamine-4-sulfatase enzyme, also known as arylsulfatase B (ARSB) (coded on locus 5q11-13) [1]. This enzyme is involved in dermatan glycosaminoglycan and chondroitin sulfates catabolism [2]. Incidence can vary among different populations and geographical regions, ranging from 1 in 238,000 births and 1 in 1,298,000 births [3]. In Colombia, of 36 known cases, 10 are in an indigenous group (Author data, not published yet). This equates to an estimated prevalence of around 0.08/100,000 inhabitants for the general population of Colombia; 2.6/100,000 indigenous people in Colombia and 3.6/100,000 indigenous people in the department of Cauca.

The *ARSB* human gene is a 209 kb gene comprised of 8 exons, ranging in size from 71 to 885 bp [1]. It encodes a polypeptide of 533 amino acids [1]. MPS VI results from several *ARSB* mutations, including missense, non-sense, splice site, small deletions, small insertions, insertion-deletion (indel) and large deletions [4].

New mutations are published continuously, aiming to establish a genotype-phenotype correlation. According to the Human Gene Mutation Database registry and other recent publications, 140 *ARSB* mutations and several

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polymorphisms have been identified so far in the gene sequence [3,5-15]. The mutations most commonly identified in patients (frequency greater than 10%), resulting from a single nucleotide exchange which creates missense are: c.629A>G, c.944G>A, c.1143-8T>G, c.1143-1G>C and c.1151G>A **(Figure 1)** [3,9-11,16].

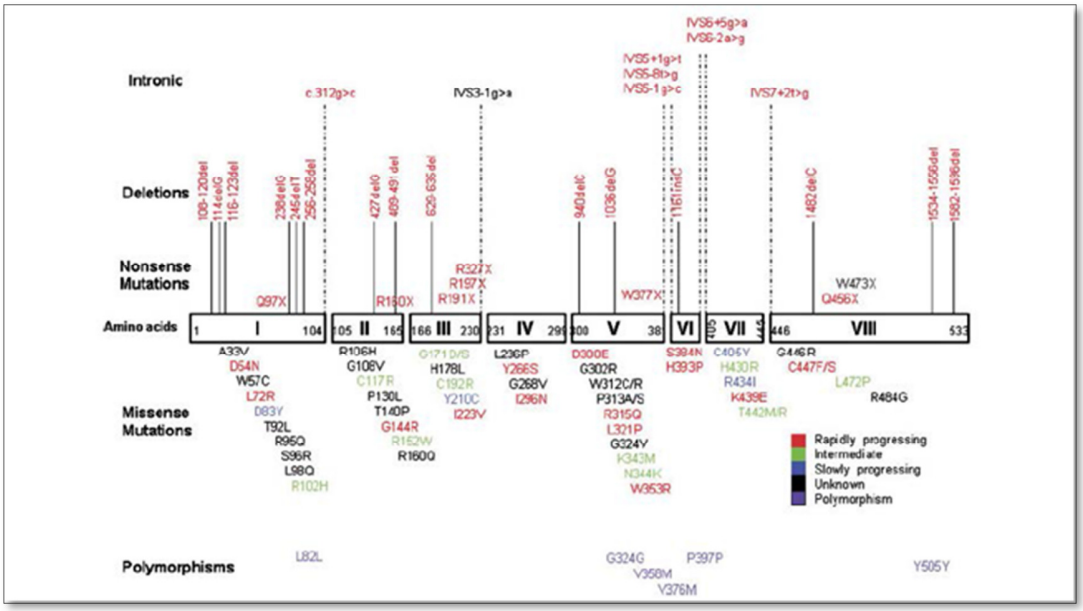

Figure 1. Mutation locations on the *ARSB* gene.
Rectangles numbered in Roman numerals represent exons and severity is color-coded on the legend [17]

A molecular study of 14 Colombian patients with MPS VI [6] identified 14 mutations (80% with severe phenotype), of which 57% had not been previously reported (p.H111P, p.C121R, p.G446S, p.*534W, p.S334I, p.H147P, c.900TNG, and c.1531_1553del) and 43% had private mutations (p.G144R, p.W322*, p.G302R, p.C447F, p.L128del and c.1143-1GNC).

The Department of Cauca in southwestern Colombia has a total population of 1,355,000 inhabitants. It is characterized by a high incidence of some genetic disorders (such as muscular dystrophies, osteogenesis imperfecta and hemoglobinopathies), probably due to the relative inbreeding and the geographical isolation of these regions. The population of this department belongs to three large ethnic groups: Afro-Colombians (22.19%), "mestizos" and white (56.31%) and the Indigenous or Amerindian groups (Paeces, Guambianos and Ingas, among others) (21.5%). These indigenous populations are some of the largest in the country (28.7% of the total national indigenous population). Here, we have identified a total of 16 cases out of the 36 reported in Colombia for MPS type VI (45% of the cases recorded in this country) (Author data, not published yet). The frequency reported may be higher, as many patients are not diagnosed or die before a definitive diagnosis is made.

The main objective of this study is to characterize, by molecular genetics, two patients identified in southwestern Colombia with the severe form of MPS type VI.

MATERIALS AND METHODS

Sample and family data collection

All the 16 patients found in the Department of Cauca have been characterized clinically and confirmed by means of enzymatic activity test in leukocytes. Two of these patients, coming from the municipalities of Totoró and Piendamó, were considered index cases for assessment and clinical care under our study in the Pediatrics Service of San José University Hospital in Popayan, Cauca. After obtaining the authorization of the institutional Ethics Committee and the informed consent from the father, mother or legal guardian of the children, a molecular characterization of the mutation was performed on the index cases (DNA extraction, PCR amplification and gene sequencing (ABI PRISM*3100 Genetic Analyzer) for each exon).

RESULTS

A single nucleotide (p.C447F) pathogenic transversion producing a sense change mutation was found in the two index cases on exon 8 of the *ARSB* gene, using the ALAMUT software (version 2). This gives rise to the exchange of one amino acid for another on the minor domain of the enzyme: position 206,029 (T/T) TGT>TTT; mutation p.C447F **(Figures 2 and 3)**.

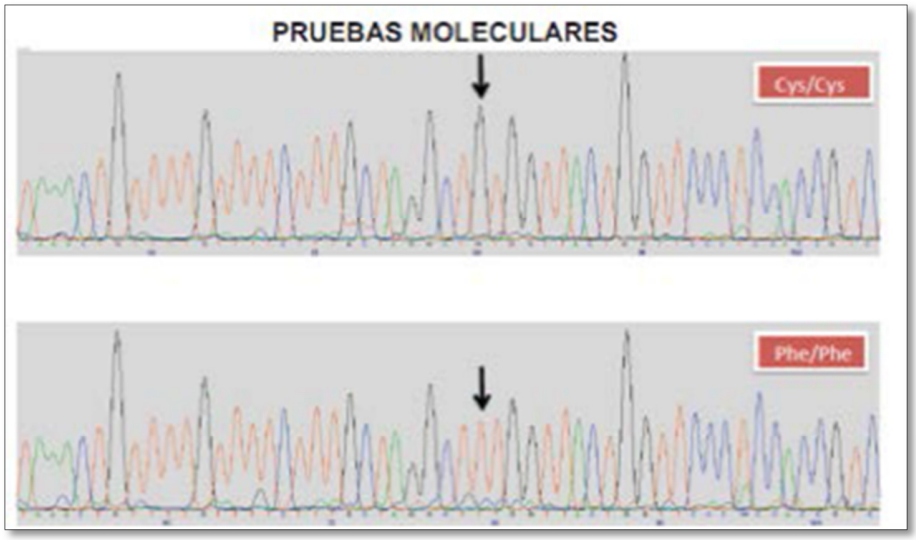

Figure 2. Molecular test: Electropherogram of the index cases [18].

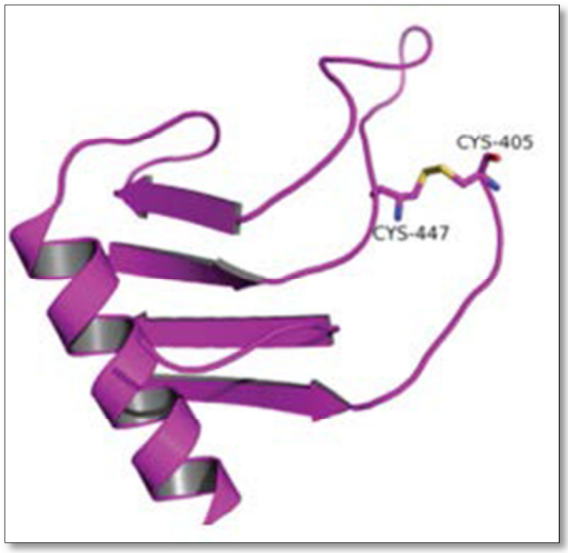

Figure 3. Crystallographic structure of the arylsulfatase minor domain: Theoretical structure proposed for sulfatase B with the Cys477Phe mutation described [18].

DISCUSSION

In the crystallographic structure of the enzyme (PDB code 1FSU), the lateral chain of the C447 amino acid appears as forming a disulphide bridge with the lateral chain of the Cys405 amino acid. This is an important secondary structural element, and when it is lost in the p.C477F mutation, it affects the folding ability of this domain and, consequently, its secondary structure.

The biological function of the minor domain appears to be related with enzyme solubility, molecular recognition of the substrates to be hydrolyzed and bioavailability in the different organs, cells and intracellular media. The mutation described results in a structural change in the minor domain, with a loss of enzyme selectivity for its substrates, as well as for changes in its solubility in the different biological media, resulting in different bioavailability when compared to the native protein. The three-dimensional structure of the major domain (amino acids 1-382) should not be affected by this mutation. Nevertheless, these functions must be severely affected by the mutation as a result of the structural change in the minor domain. This should lead to a loss of selectivity of the enzyme for its substrates.

An unusual frequency of genetic diseases is found in the department of Cauca in Colombia, which is probably underestimated due to misdiagnosis, lack of diagnosis and patients dying before diagnosis. In this study, the two index patients exhibit the same mutation, suggesting the possibility

of a common ancestral allele, probably due to the relative inbreeding and the geographical isolation of these regions. The above highlights the importance of public health policies in our country, genetic counseling, neonatal screening and identification of new cases in areas where incidence is above average.

CONCLUSION

The two index cases from different municipalities present the same homozygous p.C447F mutation. Given the low rate of migration and high frequency of endogenic marriages; the finding of the same mutation, suggests the possibility of a common ancestral allele and enhances the importance of molecular diagnosis in the study of gene hereditary diseases, allowing genotype-phenotype correlation which may predict severity and enzyme replacement success.

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