# Deep phenotyping of slowly progressive MPS VI: Insights from the French-Brazilian cohort

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## Introduction.

MPS VI is a rare autosomal recessive lysosomal disorder caused by *ARSB* mutations, leading to dermatan sulfate accumulation. Clinical presentation is variable, from severe early-onset forms to milder, slowly progressive types. Milder forms are often diagnosed later, show lower GAG levels and milder symptoms, but remain poorly described. This study aims to better characterize their phenotype and genetic variants in the context of expanded newborn screening.

## Patients and methods.

We conducted a retrospective, multinational study with French and Brazilian clinicians managing MPS VI. Inclusion criteria were: MPS VI confirmed by biochemical and molecular diagnosis, age at diagnosis >5 years, and current height >120 cm. Clinical, biological, and demographic data were collected using a standardized case report form. Clinical history was categorized into five domains: cardiovascular, ENT/pulmonary, ophthalmological, orthopedic, and visceral. Laboratory data included urinary GAG levels, qualitative GAG profile, and residual ARSB activity. Genetic variants were analyzed using PyMOL and FoldX 5.0. For patients on enzyme replacement therapy (ERT), data were recorded at initiation and last follow-up.

## Results.

We included three female and three male patients from four unrelated, non-consanguineous families. At the time of inclusion, mean age was 31 years (11-57 ), with two patients under the age of 18. All were able to walk independently. Mean age at diagnosis was 27 years (9-49). Height at diagnosis ranged from 133 to 152 cm.

Clinical data are summarized in table 1. All patients presented with skeletal abnormalities and valvular heart disease. Recurrent otitis media was reported in three patients, and carpal tunnel syndrome was present in four. Three patients had ophthalmologic involvement, although none showed corneal clouding. Urinary GAG levels were below 200 µg/mg creatinine in all but one patient. Residual ARSB enzyme activity ranged from 2.9% to 13.6% of normal.

Five patients were treated with ERT, but only one presented infusion reactions. All patients increased their weight after ERT inititation, and both patients <18y increased their height as well.

Regarding genetic analysis, all patients were compound heterozygous, and 8 different variants were identified (table 1), including the novel c.1514A>G; p.(Tyr505Cys), and the c.847G>C; p.(Ala283Pro) which was reported previously only once in a French MPS VI patient. Both variants had the Gibbs free energy decreased in relation to the wild type. 3D modeling of the p.Ala283Pro, p.Phe331Ser and p.His393Pro variants are depicted in figure 1.

| Patient | Clinical data | | | | | ARSB variants |
|---|---|---|---|---|---|---|
| | Cardiovascular | ENT/Pulmonary | Ophthalmological | Orthopedic | Visceral | |
| P1 | Valvular disease | Recurrent otitis<br>Sleep apnea | | Skeletal deformities<br>Joint stiffness<br>Carpal tunnel syndrome | Umbilical hernia | c.847G>C p.(Ala283Pro)<br>c.1178A>C p.(His393Pro) |
| P2 | Valvular disease | Sleep apnea | Corneal dystrophy | Skeletal deformities<br>Joint stiffness<br>Carpal tunnel syndrome | Umbilical hernia | c.847G>C p.(Ala283Pro)<br>c.1178A>C p.(His393Pro) |
| P3 | Valvular disease | | | Joint stiffness<br>Carpal tunnel syndrome | Umbilical hernia | c.1214G>A p.(Cys405Tyr)<br>c.937C>G p.(Pro313Ala) |
| P4 | Valvular disease | | | Carpal tunnel syndrome<br>Joint stiffness | | c.899-1G>C<br>c.629A>G p.(Tyr210Cys) |
| P5 | Valvular disease | Recurrent otitis | Myopia<br>Astigmatism | Skeletal deformities<br>Cervical spinal canal stenosis | Inguinal hernia | c.427del p.(Val143Serfs*41)<br>c.1514A>G p.(Tyr505Cys) |
| P6 | Valvular disease | Recurrent otitis | Myopia | Skeletal deformities<br>Cervical spinal canal stenosis | Inguinal hernia | c.427del p.(Val143Serfs*41)<br>c.1514A>G p.(Tyr505Cys) |

**Table 1** : Clinical and genetic data of 6 patients with slowly progressive MPS VI.

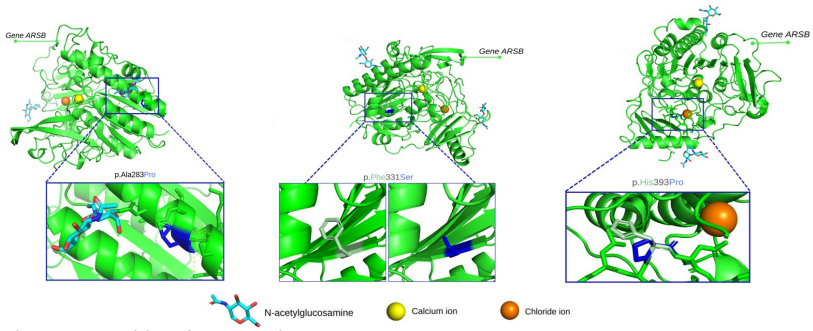


**Figure 1** : 3D modeling of variants in the ARSB gene.
3D modeling of the p.Ala283Pro, p.Phe331Ser and p.His393Pro variants (RCSB PDB: IFSU) in PyMol software with structural repair in FoldX 5.0.

## Discussion/Conclusion.

This case-series underscores diagnostic challenges posed by slowly progressive MPS VI, often leading to significant diagnostic delays despite typical disease manifestations. Although these patients may not present with some classical features such as corneal clouding or short stature, skeletal abnormalities and valvular heart disease remain consistent as early indicators. The identification of eight different *ARSB* variants, including one novel (c.1514A>G; p.Tyr505Cys) and one rare (c.847G>C; p.Ala283Pro) variant, contributes to the expanding genotypic spectrum of MPS VI. The recurrence of the c.847G>C variant in unrelated French patients raises the possibility of a regional founder effect. Our findings highlight the importance of increased awareness and targeted genetic testing to improve early recognition and management of slowly progressive MPS VI, particularly in the era of newborn screening.

*The authors have no COI to declare*