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Molecular diagnosis of spinal muscular atrophy: Experience in a pediatric hospital in Argentina

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ABSTRACT

Introduction. Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by the loss of the *SMN1* gene, with a variable clinical spectrum determined primarily by the number of copies of the *SMN2* gene. The development of new therapies underscores the importance of early molecular diagnosis and genotype-phenotype characterization.

Objective. To describe 27 years of experience in the molecular diagnosis of SMA at a pediatric referral hospital in Argentina and to evaluate the correlation between *SMN2* copy number and the SMA types.

Population and methods. A retrospective descriptive study was conducted on 1060 pediatric patients with clinically suspected SMA who were evaluated between 1997 and 2024. Molecular diagnosis was performed using PCR-RFLP and, since 2012, MLPA to determine *SMN1* and *SMN2* copy number. Genotype-phenotype correlation was evaluated in 260 patients with complete clinical characterization.

Results. The diagnosis was confirmed in 513 patients. A homozygous deletion of the *SMN1* gene was detected in 99.6% of unrelated cases. The positivity rate increased over time. A significant correlation was observed between the number of *SMN2* copies and the type of SMA, with milder phenotypes associated with a higher number of copies.

Conclusion. Molecular diagnosis of SMA enabled accurate and timely characterization of patients, avoiding invasive procedures and optimizing therapeutic decision-making. Genotype-phenotype correlation is a fundamental tool for prognosis and clinical management, highlighting the importance of an interdisciplinary approach.

Keywords: *spinal muscular atrophy; molecular diagnosis; genetic association studies; SMN complex proteins; Argentina.*

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INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by progressive muscle weakness and atrophy due to the degeneration of motor neurons in the anterior horn of the spinal cord. It is one of the most prevalent serious inherited disorders in childhood; it is inherited in an autosomal recessive pattern and has an estimated global incidence of 1 in 11 000 live births. It is characterized by a continuous clinical spectrum in which different types—from 0 to IV—are recognized, defined based on the age of symptom onset and the motor milestones achieved. These types range from early-onset forms with limited life expectancy to adult-onset forms in which the ability to walk is preserved.[1,2]

At the molecular level, this disease was described in 1995 as caused by loss of the *SMN1* (survival of motor neuron 1) gene, located at locus 5q13, which encodes the SMN protein.[3] Ninety-five percent of patients with SMA present a homozygous deletion of the *SMN1* gene involving exon 7; about 5% have a deletion on one allele and a point variant on the other (compound heterozygotes), and less than 1% of patients harbor point variants on both alleles. Located near the *SMN1* gene is *SMN2*, a highly homologous gene that, unlike *SMN1*, produces only about 10% of functional SMN protein (whose transcript lacks exon 7) (*Figure 1*).[4] The number of copies of *SMN2* varies among individuals, it is recognized as the primary modifier of the phenotype in patients with SMA, with an inverse correlation between clinical severity and the number of *SMN2* copies.[1]

In recent years, the treatment of SMA has seen significant therapeutic advances with strategies aimed at increasing levels of functional SMN protein, including *SMN2* splicing modulators, which promote the inclusion of exon 7 and result in the production of a more stable protein, and gene therapy, which introduces a functional copy of *SMN1*. Consequently, not only is early diagnosis essential, but so is quantifying the number of *SMN2* copies, since this factor constitutes a key biomarker for establishing an appropriate and timely treatment plan.[5]

In the quest for a definitive and less invasive diagnosis, in 1997 our hospital began offering molecular testing for SMA as one of the first assays provided by the Molecular Biology Laboratory, using traditional molecular techniques instead of muscle biopsy.

In this context, the objective of this study was to describe 27 years of experience in the molecular diagnosis of SMA at a pediatric referral hospital in Argentina and to perform a genotype-phenotype correlation between *SMN2* gene copy number and the type of SMA in a group of patients with detailed clinical characterization.

POPULATION AND METHODS

Patients

This is a retrospective, descriptive study of 1060 pediatric patients in Argentina with clinically suspected SMA whose samples were submitted to the Molecular Biology and Genetics Laboratory at Hospital Garrahan (HG) from July 1997 through June 2024. For this study, we used a database of all patients who underwent molecular testing in our laboratory. The study included patients treated in the Neurology Department at HG and those referred from other centers throughout the country.

Of the total number of patients studied, we determined the number of cases with positive and negative molecular test results for SMA; we also assessed their place of residence and their distribution throughout the country. To this end, for patients at our institution, we used data from the hospital's system when available. For patients referred from other centers, we analyzed the records from the Hospital's Remote Communication Office (OCD, by its Spanish acronym). Beginning in 2008, the clinical characterization of hospital patients was performed by the interdisciplinary team of the Hospital Garrahan Program for Care, Teaching, and Research on Patients with Neuromuscular Diseases (PADI-ENM; by its Spanish acronym), according to the criteria of the International SMA Consortium.[6] Patients were classified as Type I, II, and III. For genotype-phenotype correlation, 260 patients evaluated and followed at HG were included; these patients had complete clinical data and an age range, at the time of sample collection, between 1 day and 21 years.

This study was approved by the Ethics Committee of the Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan (project number 608, 2009).

DNA extraction methodology

Genomic DNA was isolated from peripheral blood leukocytes using salt precipitation until 2019,[7] and thereafter using an automated method based on M-PVA magnetic bead technology with a Chemagic™360 system.[8]

Molecular studies

Molecular diagnosis was performed using PCR-RFLP (polymerase chain reaction – restriction fragment length polymorphism), which detects the homozygous deletion of exons 7 and 8 of the *SMN1* gene, as described by van der Steege et al.,[9] with a turnaround time at our center of 3 to 5 days. This method cannot detect heterozygotes for the deletion or point variants. To study the copy number of *SMN1* and *SMN2*, the MLPA (multiplex ligation-dependent probe amplification; SALSA-Probe-Mix-021™, MRC-Holland) technique was introduced in 2012. The search for point variants was performed using Sanger sequencing (Genetics Service, Hospital de la Santa Creu i Sant Pau, Barcelona) (*Figure 2*).[10]

Statistical analysis

The overall positivity rate was determined, as well as the positivity rates for patients at the HG and those referred from other centers.

To assess differences between the two groups, a chi-square test was performed. The correlation between the number of *SMN2* copies and the types of SMA was analyzed using Spearman's correlation (IBM SPSS™ Statistics software). A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Descriptive analysis of the population

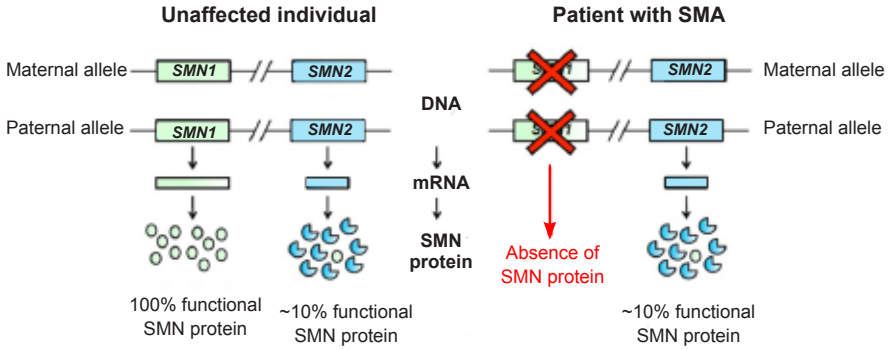
During the study period, our laboratory received 1060 samples from patients with suspected SMA, 682 of which were requested by professionals at our institution and 378 were referred from other centers in the country. Positive results for SMA were observed in 513 cases. The overall positivity rate during the study period was 48.4%; it was significantly higher in samples requested by professionals at our institution than in those referred from other centers (55.1% vs. 36.2%; p <0.0001).

The patients' place of residence was available for 730 cases. Geographic analysis showed that most patients were from the Province of Buenos Aires (PBA), followed by the Autonomous City of Buenos Aires (CABA, by its Spanish acronym), Chaco, Santa Fe, and Entre Ríos. The provinces with the fewest cases were San Luis, Tierra del Fuego, and La Rioja (*Table 1*).

Of the 513 patients who tested positive for SMA, 487 were unrelated. Of these, 443 had a homozygous deletion of *SMN1* exons 7 and 8; 42 had a homozygous deletion of *SMN1* exon 7 only; and 2 patients were compound heterozygotes with a heterozygous *SMN1* deletion on one allele and a point variant on the other.

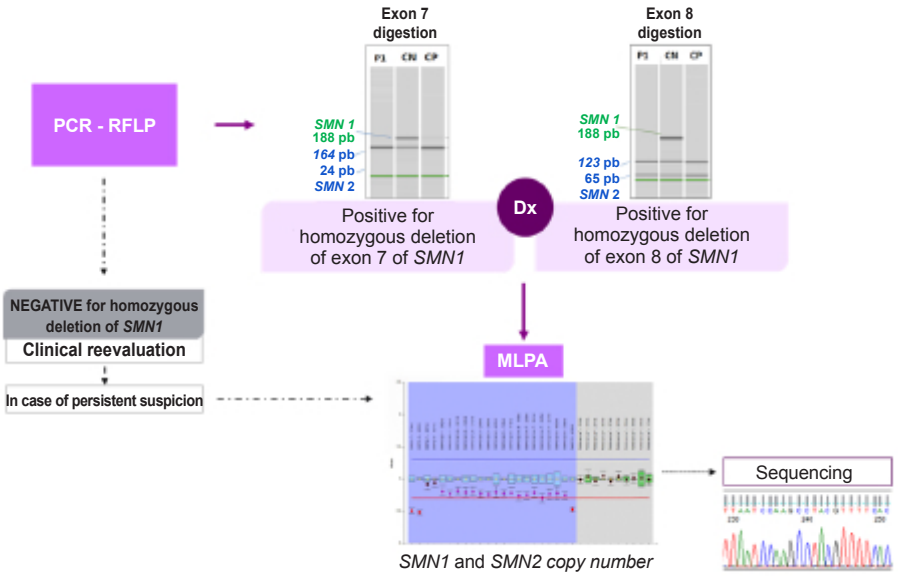
We analyzed the distribution of samples received by year and their positivity rate. The

Figure 1. Molecular mechanism of SMN protein production in unaffected individuals and in patients with spinal muscular atrophy



In an unaffected individual, the SMN1 *gene encodes 100% of the functional SMN protein. Located near* SMN1 *is* SMN2*, a highly homologous gene that differs by only 20 nucleotides. Among these, the c.840C>T variant located in exon 7 of* SMN2 *causes alternative splicing, resulting in the exclusion of this exon from most* SMN2 *mRNA transcripts. This primarily produces a truncated, non-functional form of the SMN protein, with only about 10% of the SMN protein being functional. In patients with SMA, alterations in the* SMN1 *gene result in the absence of the SMN protein derived from that gene; therefore, the presence of functional SMN protein depends entirely on production from the* SMN2 *gene. Adapted from: Spinal Muscular Atrophy UK. Splicing, Exons, and the* SMN2 *"Back-Up" Gene. SMA UK [Internet]. [Accessed on: December 26, 2025]. Available at: https://smauk.org.uk/treatments-research/nusinersen-spinraza/nusinersen-what-is-it-how-does-it-work-how-is-it-given-faqs/how-nusinersen-works/splicing-exons-smn2-backup-gene/*

Figure 2. Molecular diagnostic algorithm for spinal muscular atrophy at Hospital Garrahan



When SMA is clinically suspected, a PCR-RFLP test is initially performed to detect the homozygous deletion of exons 7 and 8 of the SMN1 *gene, which is present in approximately 95% of patients. The technique involves PCR amplification of exons 7 and 8 of the* SMN1 *and* SMN2 *genes, followed by digestion with the restriction enzymes DraI and DdeI, respectively. The digested products are analyzed by capillary electrophoresis (QIAxcel™, Qiagen), including the patient sample (P1), a negative control (CN), and a positive control (CP) for each exon. If the PCR-RFLP result is negative but clinical suspicion persists, MLPA is performed to assess heterozygous deletion of* SMN1*. In this method, the amplicons are separated by capillary electrophoresis (ABI™ 3130 and 3500 automated sequencers; Applied Biosystems), and the electropherograms are analyzed using Coffalyser.Net™ software. The MLPA image corresponds to a case with a heterozygous deletion, with one copy of* SMN1 *exons 7 and 8. The MLPA technique also allows for the determination of the copy number of the* SMN2 *gene. Finally, if MLPA detects a heterozygous deletion, the diagnosis is confirmed by Sanger sequencing. Excerpted and modified from Monges S, De Castro Pérez F, Mozzoni J, Aguerre V, Palumbo C, et al. GAP 2019: Management of Spinal Muscular Atrophy. Buenos Aires (ARG): "Juan P. Garrahan" Children's Hospital; 2019. [Accessed on January 19, 2026]. Available from: https://www.garrahan.gov.ar/images/intranet/guias_atencion/GAP_2019_-_MANEJO_AME_-_VERSION_FINAL.pdf*

number of samples received increased until approximately halfway through the study period (2012), after which a sustained decline was observed. In contrast, the positivity rate showed a gradual increase throughout the study period, with a possible turning point between 2014 and 2016 (*Figure 3*).

Genotype-phenotype correlation

Of the 376 patients with SMA at our institution, genotype-phenotype correlation was performed in 260 patients for whom complete clinical data were available. Of these, 39% were type I SMA (101 patients); 43% were type II SMA (111 patients); and 18% were type III SMA (48 patients).

The number of *SMN2* copies was distributed as follows: for SMA type I, 93 patients were identified with 2 copies and 8 with 3 copies; for SMA type II, 1 with 2 copies, 109 with 3 copies, and 1 with 4 copies; and for SMA type III, 42 with 3 copies and 6 with 4 copies.

In the analysis of the number of *SMN2* copies and its correlation with SMA type (*Figure 4*), we observed that in the group of patients with SMA type I, a large majority had 2 copies of the *SMN2* gene, with a very low percentage of patients having 3 copies. In the group of patients with SMA type II, almost all had 3 copies of *SMN2*. Finally, in the group with SMA type III, although the majority of patients had 3 copies, a significant increase was observed in the percentage of patients with 4 copies. Upon statistical evaluation of the relationship between the number of *SMN2* copies and the type of SMA: We found a significant genotype-phenotype correlation (Spearman's correlation: $\rho = 0.855$; $p < 0.0001$), with a milder phenotype observed as the number of *SMN2* copies increased.

DISCUSSION

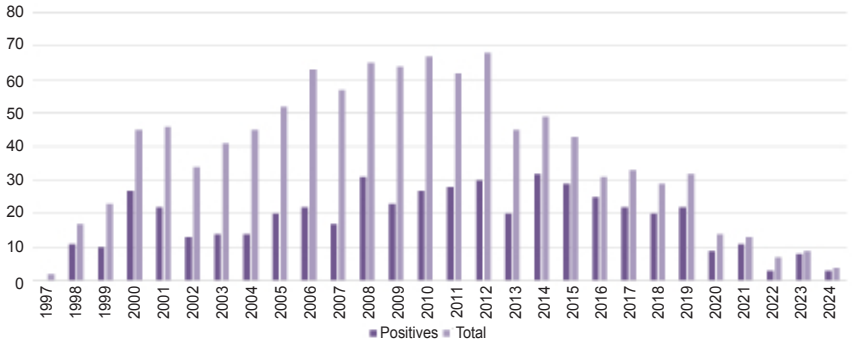
In this study, we describe a 27 years experience in the molecular diagnosis of SMA in a series of pediatric patients evaluated at a public

Table 1. Percentage distribution of place of residence among 730 patients with suspected spinal muscular atrophy studied at Hospital Garrahan from July 1997 to June 2024

Province	n° of cases	Percentage (%)
Buenos Aires	288	39.5
CABA	115	15.8
Chaco	56	7.7
Santa Fe	51	7.0
Entre Ríos	47	6.4
Tucumán	29	4.0
Misiones	26	3.6
Santiago del Estero	20	2.7
Mendoza	16	2.2
Córdoba	12	1.6
Corrientes	12	1.6
Río Negro	10	1.4
Formosa	10	1.4
Santa Cruz	7	1.0
San Juan	6	0.8
Chubut	5	0.7
Jujuy	5	0.7
Neuquén	4	0.5
La Pampa	3	0.4
Catamarca	3	0.4
Salta	2	0.3
San Luis	1	0.1
Tierra del Fuego	1	0.1
La Rioja	1	0.1
TOTAL	730	100.0

CABA: Autonomous City of Buenos Aires (by its Spanish acronym).

Figure 3. Distribution of cases with suspected spinal muscular atrophy: positive cases and total cases over time



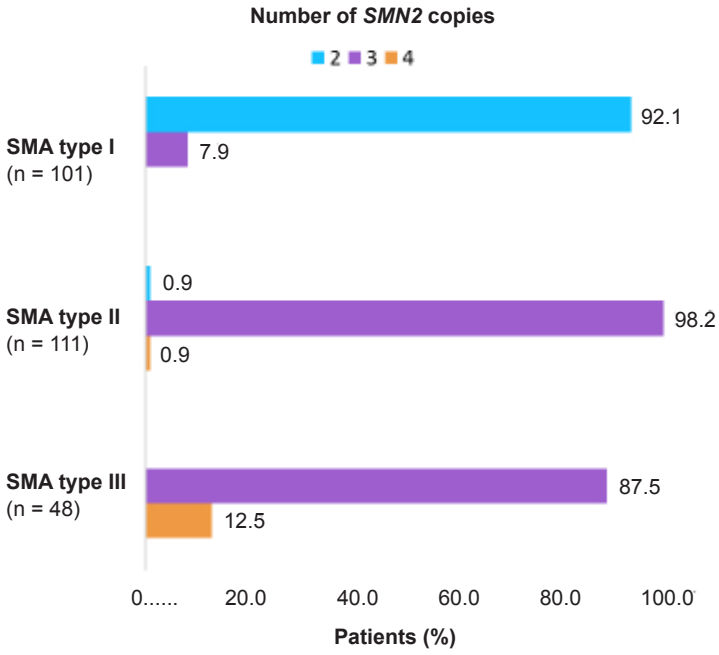
Overall distribution of patients by year: of a total of 1060 patients studied, 513 were positive for SMA. The graph shows the total number of patients with suspected SMA by year (light purple bars), as well as the number of SMA-positive cases by year (dark purple bars).

referral hospital in Argentina.

During this period, we were able to confirm a diagnosis of SMA in 513 children.

The PCR-RFLP technique is a useful diagnostic tool because of its speed and, unlike MLPA, it does not require a minimum number of samples for processing; however, it cannot detect heterozygous deletions or point mutations. Using PCR-RFLP, we were able to diagnose 99% of patients with SMA, and it was only necessary

Figure 4. Distribution of *SMN2* copies by type of spinal muscular atrophy



Spearman's correlation: ρ = 0.855; p <0.0001.

to expand the diagnostic algorithm for the remaining 1%.

An analysis of the place of residence of the study population provides some insight into the nationwide distribution of SMA patients. Most cases were from PBA and CABA, regions with higher population density[11] and proximity to the hospital.

As a national, high-complexity pediatric hospital and a referral center for SMA, we were pioneers in the diagnosis and follow-up of these patients, promoting diagnostic accuracy in the ordering of molecular testing. This is reflected in an increase in the positivity rate over time, not only among patients at our hospital but also among those referred from other institutions across the country. When evaluating the distribution of suspected SMA cases over time, we observe an overall decline in the number of samples submitted to the laboratory. This could be due to various factors: demographic factors, such as the declining birth rate—which has shown a steady decrease since 2012 and an accelerated decline beginning in 2018;[12] and other factors related to the availability and advancements in diagnostic resources. Since 1997, through various agreements, specialists from our institution have actively participated in the training of new professionals. This work may have contributed to expanding the network of professionals trained in SMA diagnosis in the country, potentially leading to decentralization of diagnosis and a reduction in the number of cases referred to our laboratory. Likewise, advances in knowledge, the availability of disease-modifying therapies, the emergence of new diagnostic centers, and molecular studies facilitated by the pharmaceutical industry may also have influenced this trend. Finally, appropriate genetic counseling for families and the incorporation of prenatal genetic testing into family planning—including options such as embryo selection or reproductive decisions—are another factor that could influence the reduction in the number of cases referred to the laboratory.

Regarding the relationship between the number of *SMN2* copies and the type of SMA, we conducted a correlation analysis in patients who were evaluated by the interdisciplinary team (PADI-ENM). In 2016, we published an initial correlation study involving 144 patients;[13] in this second study, we expanded the number of patients to 260 with a similar distribution of SMA subtypes. Consistent with the previous study and findings in other populations,[14-18] we found a strong genotype-phenotype association in which a higher number of *SMN2* copies was associated

with less severe disease; however, this correlation is not absolute, as patients with the same number of *SMN2* copies may have different phenotypes. This could be due to other modifying factors that influence SMN protein expression levels.[1,19] Most patients in our series have SMA type II with three copies of *SMN2*. Furthermore, no patients were identified with a single copy of *SMN2* or with more than four copies. The presence of a single copy of *SMN2* has been described primarily in patients with severe neonatal forms,[20,21] while more than four copies have been reported in very mild forms.[14,22,23] The absence of these cases in our series may be due to the age range of the patients treated at our hospital.

Genotype-phenotype studies in SMA and the timing of diagnosis are critical for defining the prognosis and stratification at the time of treatment selection, as well as for future clinical trials. In our series, of the total number of patients evaluated by the hospital's interdisciplinary team, 67 are being treated with splicing modulators or gene therapy. In this context, the involvement of an interdisciplinary team was key to comprehensively addressing the patients' clinical and therapeutic needs.

Finally, the potential introduction of newborn screening for SMA in Argentina could be useful for the early detection of patients at a stage when motor neuron degeneration is still in its early stages, with the potential to prevent the progression of muscle weakness and atrophy.

CONCLUSION

The introduction of molecular testing for SMA in 1997 has made it possible to offer this analysis to 1060 patients in Argentina; it was essential for avoiding invasive procedures, guiding treatment, and providing timely genetic counseling. During this period, more than 500 patients were diagnosed and molecularly characterized. Furthermore, genotype-phenotype correlation is a fundamental tool for predicting clinical course and optimizing treatment selection. ■

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