

The phenotypic spectrum and genetic determinants of severe spinal muscular atrophy in individuals with a single SMN2 copy: an international retrospective observational study



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Summary

Background Spinal Muscular Atrophy (SMA) is a phenotypically heterogeneous disease. The Survival Motor Neuron 2 (SMN2) gene copy number can partially predict the clinical severity of SMA, with a single SMN2 copy generally associated with the most severe phenotypes. The aim of this retrospective observational study was to explore the spectrum of phenotypes associated with one SMN2 copy and the possible association with genotype and outcome.

Methods We conducted a retrospective observational study of individuals with genetically confirmed SMA (biallelic Survival Motor Neuron 1 [SMN1] variants) and one SMN2 copy, recruited from 36 Italian neuromuscular centres and additional 28 centres from nine other countries (Austria, Belgium, Brazil, Chile, Germany, Netherlands, Spain, United Kingdom and United States) between January 2015 and November 2025.

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Individuals were included irrespective of age or phenotype; those with incomplete genetic data or confounding diagnoses were excluded. The primary outcome was the phenotypic spectrum associated with a single *SMN2* copy, including clinical severity, genotype, treatment exposure, and survival at last follow-up.

Findings Sixty-five individuals with one *SMN2* copy were included. Neonatal onset was observed in 50/65 (77%). The predominant phenotype was type 0 (39/50, 78%), followed by type 1.1 (6/50, 12%). Five individuals with neonatal onset had prenatal signs (reduced foetal movements and cardiac malformation), but no contractures reported. All individuals with neonatal onset had homozygous deletions of *SMN1*. The remaining 15/65 (23%) had later onset, with milder phenotypes and all but two presented either with an heterozygous *SMN1* deletion associated with a point mutation, or with c.859G>C(p.Gly287Arg) variant in *SMN2*.

Interpretation Our findings confirm that type 0 is the most frequent phenotype associated with one *SMN2* copy, but the boundaries between neonatal-onset phenotypes appear to be fluid. The individuals with one *SMN2* copy with milder phenotypes carried variants known to mitigate disease severity. Further prospective studies are needed to better define genotype–phenotype correlations and inform treatment decisions in this population.

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Keywords: Spinal muscular atrophy; One *SMN2* copy; Prenatal SMA; Type 0 SMA

Research in context

Evidence before this study

Evidence on spinal muscular atrophy (SMA) associated with a single Survival Motor Neuron 2 (*SMN2*) copy is derived from a limited and heterogeneous body of literature. We searched PubMed from inception to February 2026 using (Spinal Muscular Atrophy [MeSH Terms]) AND (1*SMN2* copy) AND (type 0) OR (prenatal SMA) NOT (review [Publication Type]) without language restrictions.

After manual exclusion according to relevance we identified approximately 20 relevant publications. These studies mainly consisted of small case series, single-centre cohorts, and aggregated genotype–phenotype analyses. Overall, the literature supports an association between a single *SMN2* copy and severe neonatal SMA phenotypes, while also reporting variability in prenatal findings and early clinical presentation. Anecdotal descriptions of milder phenotypes and of potential genetic modifiers were reported. Individuals with prenatal-onset SMA were excluded from pivotal clinical trials of disease-modifying therapies, resulting also in limited data on treatment outcomes in this subgroup.

Added value of this study

The international collaboration facilitated data collection from a large cohort of individuals with one *SMN2* copy and assessment of the spectrum of possible phenotypes associated with one *SMN2* copy. The study suggests that while the great majority of individuals with a single *SMN2* copy is associated with the most severe phenotypes, milder phenotypes are not infrequent and are associated with heterozygous *SMN1* deletions associated with a point mutation, or with positive variants.

Implications of all the available evidence

Our results suggest that a more individualised approach, focussing on both clinical features and genotyping, including modifier variants, may help to better define the heterogeneous phenotypic spectrum and provide appropriate information for counselling and possible treatment eligibility. Further prospective studies with systematic molecular characterisation and longitudinal outcome assessment are needed to better define genotype–phenotype correlations and inform treatment decisions in this population.

Introduction

Spinal muscular atrophy (SMA) is a phenotypically heterogeneous autosomal recessive disorder caused by bi-allelic pathogenic variants in the Survival Motor Neuron 1 (*SMN1*) gene, which results in a deficiency of the survival motor neuron (SMN) protein.¹ The clinical severity of SMA is partially modulated by the copy number of Survival Motor Neuron 2 (*SMN2*), a

paralogous gene that produces limited amounts of functional SMN protein due to alternative splicing of exon 7.¹ Since the assessment of *SMN2* copy number has become more easily available, several studies have reported that a single copy of *SMN2* is generally associated with type 1 SMA, the most severe phenotype,^{2,3} including the subtypes with severe signs at birth or in the neonatal period, i.e. type 1A, or 1.1 according to the

Dubowitz classification.^{4–6} The description of an even more severe phenotype with prenatal onset has further expanded the spectrum of phenotypes associated with a single copy of *SMN2*. Following the description of a few cases,⁷ Dubowitz classified as type 0 a phenotype characterised by prenatal onset, absent foetal movements, neonatal respiratory and bulbar failure, and death typically within days or weeks of life.⁸ Since the original description, several studies have reported other cases of type 0 with multisystemic involvement.^{3,9–12} Most reported cases with type 0 SMA carried only one copy of *SMN2*, but there are also sporadic reports of infants with prenatal onset and two *SMN2* copies.^{9,13} The review of the clinical signs reported in the literature highlights that not all the individuals with type 0 and a single copy of *SMN2* fulfil the criteria reported by Dubowitz in the initial classification, and that there is a variability of prenatal and postnatal features.³

This heterogeneity has raised the question of where to draw the line between infants with type 0 SMA with few antenatal signs and those with severe type 1.1, and questioned whether type 0 represents a distinct clinical entity or the severe tail of a continuous phenotypic spectrum.³ While this may appear as a merely academic discussion, the possibility to identify distinct phenotypes has a significant practical impact on possible access to the available disease modifying therapies (DMTs) that have redefined the natural history of SMA. The approval of gene addition therapy (onasemnogene abeparvovec), and splicing modulators using antisense oligonucleotide (nusinersen) or small molecules (risdiplam) has led to unprecedented survival and motor outcomes in types I–III SMA.¹ However, individuals with prenatal-onset disease were not only systematically excluded from pivotal trials^{14–16} but, in many countries also do not have access to the available DMTs.

As previously noted,³ the lack of standardised phenotypic descriptors for type 0 undermines clinical clarity and consistency across centres, and it is therefore important to define criteria to identify infants with the full typical type 0 phenotype and possible variations or overlap with the severe type 1 phenotype.

As most cases of both type 0 and 1.1 phenotypes are associated with a single copy of *SMN2*, we aimed to explore the entire spectrum of phenotypes associated with a single copy of *SMN2* as part of a collaborative international effort. More specifically, we wished to establish the different phenotypes observed in association with a single copy of *SMN2*, identifying the typical type 0 or type 1.1 phenotypes and other possible severe phenotypes not completely fitting in either group. We also aimed to detect whether less severe phenotypes could be associated with different genetic background. Furthermore, we also aimed to establish whether different severity at presentation was associated with different outcomes or different attitude to treatments offered.

Finally, in order to better establish the spectrum of type 0, we also investigated if type 0 phenotypes were present in SMA individuals with more than one copy of *SMN2*, analysing the appropriateness of the reported clinical diagnosis.

Methods

Study design

This was a two-part, retrospective observational study composed of:

- A nationwide cohort study collecting granular data from all tertiary neuromuscular referral centres in Italy.
- Integration of the Italian data with additional data as part of an international collaboration.

Individuals diagnosed and/or followed between January 2015 and November 2025 were included in the analysis. The retrospective data collection began in April 2025 and was completed in November 2025.

The Italian part of the study involved the 36 centres identified by the Regional Governments as referral centres for SMA in Italy.¹⁷ All are part of a nation-based network, the Italian SMA collaboration (ITASMAc), using an academic registry, the international Spinal Muscular Atrophy Registry (iSMAR).¹⁸ Full details of participating collaborators and centres are provided in the [Supplementary Materials \(Supplementary Table S1\)](#). As part of an international academic collaboration, data were also available from 28 other centres from nine countries (Austria, Belgium, Brazil, Chile, Germany, Netherlands, Spain, United Kingdom and United States). Full details of participating collaborators, centres, and countries are provided in the [Supplementary Materials \(Supplementary Table S2\)](#).

Ethics

For the Italian part of the study, approval was granted by the Ethics Committee of Fondazione Policlinico Universitario Agostino Gemelli IRCCS (coordinating Centre) (Date 26/05/2020; No 1894) and by all the other participating centres. Written informed consent was obtained in all participants. Full details of participating collaborators and centres are provided in the [Supplementary Materials \(Supplementary Table S1\)](#).

For the international part of the study, all local protocols were approved by institutional ethics committees or met criteria for retrospective anonymised data collection under national regulations.

Full details of participating collaborators, centres, countries, ethical approval, and consent for the International SMA Group are provided in the [Supplementary Materials \(Supplementary Table S2\)](#).

This study was performed in line with the principles of the Declaration of Helsinki.

Participants

Individuals were eligible if they had:

- Molecular diagnosis of SMA with homozygous/compound heterozygous pathogenic variants of the *SMN1* gene and confirmation of a single copy of *SMN2*, irrespective of the phenotype.
- Type 0 phenotype and more than one *SMN2* copy.

Exclusion criteria included missing or indeterminate genetic data and confounding diagnoses affecting motor function.

The determination of the *SMN2* copy number was assessed by multiplex ligation-dependent probe amplification (MLPA) assay (SALSA MLPA Probemix P021 or P060, MRC-Holland) or, in the Gemelli lab, by quantitative polymerase chain reaction (qPCR).

The assessment of additional genetic modifiers, including *SMN1* small sequence variants and *SMN2* sequence variants known to enhance exon 7 inclusion, was uniformly standardised across all Italian participating centres but not in the other countries. While some laboratories routinely performed extended molecular analyses beyond *SMN1* deletion testing and *SMN2* copy number determination, in other centres additional sequencing was undertaken at the discretion of the treating clinicians, particularly in cases with phenotypic features not fully consistent with the expected severity.

Data collection

In Italy data is collected through a structured academic registry (iSMAR), established in 2016, with prospective and retrospective data collection from participating centres. Data entry follows a predefined data dictionary; however, completeness of specific variables may vary, particularly for historical cases diagnosed before the availability of disease-modifying therapies. Information on respiratory management, feeding support and treatment exposure was available in the majority of cases, although the level of detail (e.g., type of ventilatory interface, formal respiratory function assessments) was not uniformly captured across centres, especially for earlier cases.

For the international cohort, data were obtained from established neuromuscular centres with local data collection systems; however, heterogeneity in documentation practices may limit direct comparisons of supportive care strategies across countries.

A shared data dictionary and centralised database were used for harmonised data entry. Variables were grouped into six structured domains:

- Prenatal History: amniotic fluid volume, foetal movement reports.
- Neonatal Presentation: gestational age, hypotonia, weakness, contractures, bulbar dysfunction, respiratory status, time to mechanical ventilation.

- Treatment Exposure: type and timing of DMTs, prenatal interventions (if applicable).
- Supportive Measures: ventilation type, nutritional support, tracheostomy.
- Outcome Data: age at death or last follow-up, motor milestones, complications.

Motor functional scores, where available, were assessed using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) or the Hammersmith Functional Motor Scale Expanded (HFMSSE).

Sex was recorded for all participants as part of the baseline demographic variables in accordance with the Sex and Gender Equity in Research (SAGER) reporting recommendations.

Based on the existing literature, clinical signs were analysed to establish whether they fitted in the two main phenotypes described in association with a single copy of *SMN2*. Phenotypic classification was based on the Dubowitz clinical framework for childhood SMA and subsequent literature addressing the most severe prenatal/neonatal presentations.^{4-6,8} Operational definitions were agreed a priori within the collaborative group and applied centrally using reported prenatal history and neonatal clinical features (contractures, bulbar and respiratory involvement), rather than *SMN2* copy number alone, reflecting the study goal of decoupling molecular prediction and phenotype. The phenotypes with neonatal onset were classified as follows:

- Type 0: Prenatal-onset SMA with reduced foetal movements with or without or polyhydramnios. Presence of contractures at birth, associated with severe hypotonia and respiratory and/or bulbar dysfunction.⁸
- Type 1.1 (or 1A): Severe neonatal-onset SMA presenting at birth or within the first month of life, without contractures or other evidence of prenatal onset such as reduced foetal movements⁴⁻⁶
- Intermediate neonatal phenotypes: Individuals who did not fully meet criteria for classical type 0 but had some antenatal signs that would not allow them to be classified as type 1.1 were categorised as “intermediate neonatal phenotypes” for the purposes of this study. This designation reflects clinical overlap rather than a formally recognised subtype.
- Other phenotypes with onset after the neonatal period were classified according to the Dubowitz criteria (1.5, 1.9, type 2 etc)⁴⁻⁶

Supplementary Table S3 provides a summary of operational categories applied in the present study.

Statistical analysis

Participants were included if they met the predefined eligibility criteria described in the Participants section.

Briefly, inclusion criteria comprised a genetically confirmed diagnosis of 5q spinal muscular atrophy and availability of sufficient clinical information to allow reliable phenotypic classification. Patients with insufficient clinical data preventing reliable classification were excluded.

Descriptive statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Continuous variables are presented as median and range, and categorical variables as counts and percentages.

Given the retrospective and descriptive nature of the study, no formal hypothesis testing or inferential statistical analyses were performed, and no sample size calculation was undertaken.

Outcomes were defined a priori based on the study objectives and included phenotypic classification, genotype, treatment exposure, and survival at last available follow-up. No sensitivity or post-hoc analyses were performed.

Role of the funding source

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Biogen, Roche and Novartis Gene Therapies provide financial support for the SMARtCARE registry in Germany and Austria and for iSMac in Italy, UK and USA. The funders had no role in the design and conduct of the study, interpretation of the data and the decision to submit the manuscript for publication.

Results

Cohort with a single copy of SMN2

All Italian centres provided data. This included 21 individuals with a single copy of *SMN2*, 15 of which had neonatal onset, two had onset after the neonatal period but within 6 months from birth, and the remaining four had later onset and a milder phenotype. Only 13/21 (61%) Italian individuals with one *SMN2* copy described in this study were still in the registry at last assessment (December 2025) as the remaining 8/21 (39%) did not survive. The current 13 patients represent 0.9% of the totality of the Italian registry (1335 SMA). The international cohort included 44 individuals with one *SMN2* copy with 27 individuals with neonatal onset and 17 with later onset and milder phenotype. Details are provided in Fig. 1.

The overall cohort included 65 individuals carrying a single *SMN2* copy. 55.7% were males and 44.3% were

females. Sex distribution was reviewed across the cohort and did not show any evident imbalance or phenotype-specific differences.

The description of the individual phenotypes will be discussed collectively, with granular details provided in Tables 1–3.

Of the 65 individuals, 50/65 (77%) presented with neonatal onset, 2/65 (3%) showed a disease onset after the neonatal period but within 6 months from birth and the remaining 13/65 (20%) had later onset and milder phenotypes.

Fig. 2 provides details on the whole cohort, with phenotype, DMT treatment and survival.

Neonatal onset: type 0

Among the 50 individuals presenting with neonatal onset, 39/50 (78%) presented a classical type 0 phenotype with prenatal onset with contractures at birth (in 27/39, 69%, associated with reduced foetal movements and in 6/39, 15%, with polyhydramnios), prominent weakness and hypotonia, and both respiratory and bulbar involvement at birth. Twenty-two of the 50 infants (44%) also presented congenital cardiac malformations.

Thirty-two of the 39 (82%) individuals were not treated with DMTs and died between the age of 0 and 14 months (median: 14 days, mean: 93 days). The remaining 7/39 (18%) received treatment with DMTs and 6/7 (85.7%) were alive at the last follow-up with a median age of 4.4 years (range 5 months–9 years). The last treated individual died at the age of 5 months due to cardiac arrest. Among treated individuals without tracheostomy at treatment initiation, outcomes included death, progression to tracheostomy, or limited motor milestone acquisition such as head control and independent sitting.

Individual details of these individuals are provided in Table 1 (ID 1–39).

Neonatal onset: type 1.1/1A

Six individuals of 50 (12%) presented with a type 1.1/1A phenotype, with severe weakness and hypotonia at birth or in the first month but no evidence of contractures associated with reduced foetal movements, or other prenatal signs. Four individuals were not treated with DMTs and 2/4 (50%) died at 23 and 90 days from birth. Two individuals of six (33%) received DMTs and were alive at last available follow-up aged 10 and 12 years, respectively. Individual details of these individuals are provided in Table 1 (ID 40–45).

Neonatal onset: intermediate phenotypes

Five children of 50 (10%) had neonatal onset with weakness and hypotonia and had no contractures but reportedly reduced foetal movements.

Individual details of these individuals are provided in Table 1 (ID 46–50).

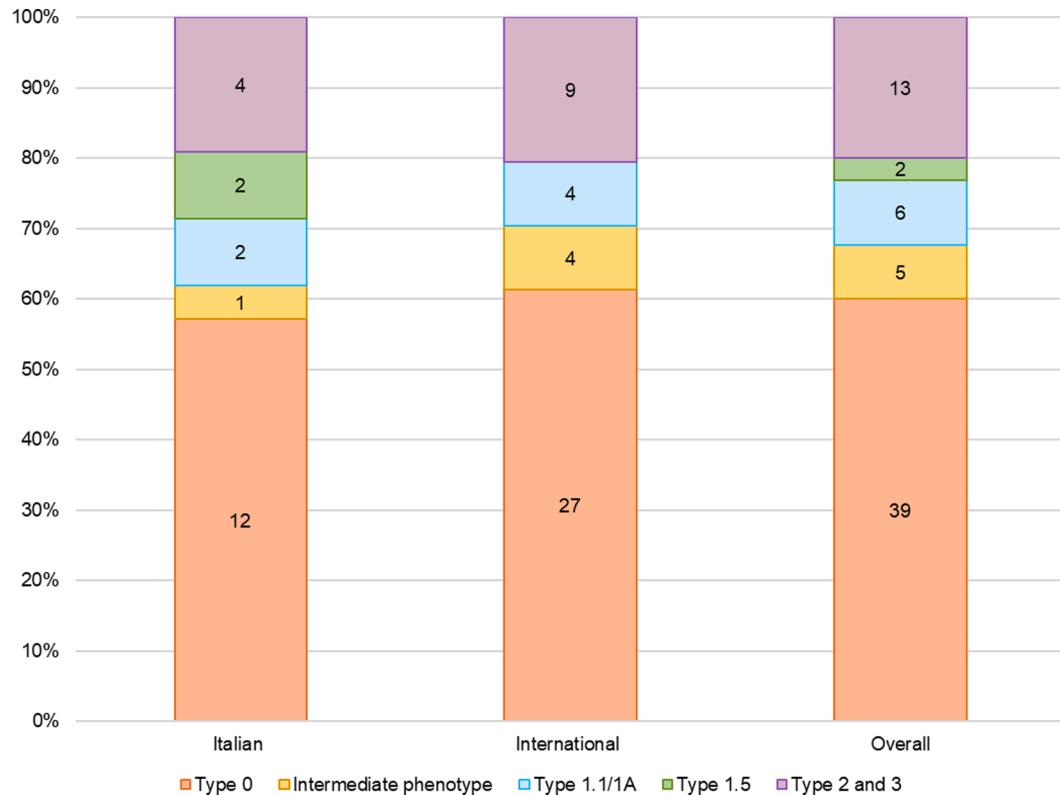


Fig. 1: Distribution of phenotypes with one *SMN2* copy.

Later onset: type 1.5

Two individuals out of 65 (3%) had onset after 3 months with weakness and hypotonia.

Detailed individual outcomes and genotypes are reported in [Table 2](#) (ID 51–52).

Later onset: type 2 and 3

Thirteen individuals (five type 2 and eight type 3) had a disease onset after 6 months. All of them achieved head control at a median age of 3 (range 2–4 months) months and independent sitting at a median age of 6 (range 6–9 months) months. Three out of 13 (23%) required invasive respiratory support (tracheostomy) and feeding support. Among individuals with milder phenotypes, *SMN1* sequence variants or *SMN2* variants, including c.859G>C (p.Gly287Arg), were observed.

Detailed individual outcomes and genotypes are reported in [Table 2](#) (ID 53–65).

Cohort of type 0 with more than one *SMN2* copy

Seven additional infants were reported as having a classical type 0 phenotype associated with more than one *SMN2* copy. Three individuals were recruited in the Italian cohort and the remaining four in the international. All of them carried two *SMN2* copies. All

presented contractures and reduced foetal movements associated with prominent weakness and hypotonia together with respiratory impairment at birth. Five of the seven (71%) presented with congenital cardiac malformations.

Six of seven (86%) individuals were treated with DMTs and were alive at last available follow-up with a median age of 16 months (range 10 months–10.5 years).

Individual details of these individuals are provided in [Table 3](#) (ID 66–72).

Discussion

While a lot of attention has been devoted to the SMA phenotypes associated with 2 and 3 *SMN2* copies^{22–25} and, more recently also to 4 copies,^{26–28} less has been reported about the clinical spectrum associated with a single copy of *SMN2*. Most studies report the association between a single copy of *SMN2* and the most severe phenotypes with neonatal onset, not always providing details of whether there were antenatal signs consistent with type 0². Occasional descriptions of a single copy of *SMN2* have also been reported in association with milder phenotypes.² We report a large series of SMA individuals with one *SMN2* copy with

ID	Sex	DMT treatment	Last follow up	Respiratory management	NG/G Tube	Early movements/milestones	CHOP	Genotype		Additional features
								SMN1	SMN2	
Untreated Italian type 0										
1	M	no	Died at 5 d	NIV >16 h	yes	None	-	del/del	-	Preterm 35 + 5
2	F	no	Died at 13 d	NIV >16 h	yes	None	4 (1w)	del/del	-	-
3	M	no	Died at 21 d	NIV >16 h	yes	None	-	del/del	-	-
4	M	no	Died at 34 d	NIV >16 h	yes	None	-	del/del	-	CM
5	M	no	Died at 41 d	NIV >16 h	yes	None	2 (birth)	del/del	-	CM
6	F	no	Died at 52 d	NIV >16 h	yes	None	3 (birth); 0 (2 m)	del/del	-	-
7	F	no	Died at 68 d	Tracheo (33 d)	yes	AM (1 m)	16 (birth); 9 (2 m)	del/del	-	CM; CNSM
Untreated type 0 international										
8	F	no	Died at 4 d	NIV >16 h	no	None	0 (birth)	del/del	-	CM; CNSM
9	F	no	Died at 6 d	NIV >16 h	no	None	-	del/del	-	-
10	F	no	Died at 6 d	NIV >16 h	no	None	-	del/del	-	CM
11	F	no	Died at 6 d	NIV >16 h	no	None	-	del/del	-	-
12	F	no	Died at 6 d	NIV >16 h	no	None	-	del/del	-	-
13	M	no	Died at 7 d	NIV >16 h	no	None	-	del/del	-	CM
14	F	no	Died at 8 d	NIV >16 h	no	None	0 (birth)	del/del	-	-
15	M	no	Died at 9 d	NIV >16 h	no	None	-	del/del	-	CM
16	F	no	Died at 11 d	NIV >16 h	no	None	-	del/del	-	CM
17	M	no	Died at 11 d	NIV >16 h	no	None	-	del/del	-	-
18	M	no	Died at 11 d	NIV >16 h	no	None	-	del/del	-	CM
19	M	no	Died at 12 d	NIV >16 h	no	None	-	del/del	-	CM; CNSM
20	F	no	Died at 13 d	NIV >16 h	no	None	2 (birth)	del/del	-	-
21	M	no	Died at 14 d	NIV >16 h	no	None	-	del/del	-	-
22	M	no	Died at 19 d	NIV >16 h	no	None	-	del/del	-	-
23	M	no	Died at 21 d	NIV >16 h	no	None	-	del/del	-	CM; CNSMs
24	M	no	Died at 26 d	NIV >16 h	no	None	-	del/del	-	Preterm 35 + 2
25	F	no	Died at 36 d	NIV >16 h	yes	None	-	del/del	-	-
26	M	no	Died at 49 d	NIV >16 h	no	None	0 (birth); (49 d)	del/del	-	-
27	F	no	Died at 2 m	NIV >16 h	no	None	8 (birth); 0 (2 m)	del/del	-	CM
28	F	no	Died at 3 m	NIV >16 h	no	None	0 (birth)	del/del	-	CM; CNSM
29	F	no	60 m	Tracheo (2 m)	yes	None	0 (60 m)	del/del	-	CM; CNSM
30	M	no	Unk	NIV >16 h	no	None	-	del/del	-	CM
31	M	no	Died at 14 m	Tracheo (2 m)	yes	None	6 (birth)	del/c.815A>G p.(Tyr272Cys)	-	CM
32	M	no	Died at 1 m	NIV >16 h	yes	None	4 (birth)	del/del	-	-
Treated Italian type 0										
33	F	R (10 d)	5 m	NIV <16 h	yes	AM	4 (10 d); 25 (2 m)	del/del	-	Preterm 31 + 3; CM
34	M	N (13 d)	Died (5 m)	Tracheo (3 m)	yes	AM	0 (1w); 9 (3 m)	del/del	-	Preterm 35; CM

(Table 1 continues on next page)

ID	Sex	DMT treatment	Last follow up	Respiratory management	NG/G Tube	Early movements/milestones	CHOP	Genotype		Additional features
								SMN1	SMN2	
(Continued from previous page)										
35	M	N (1 m)	25 m	Tracheo (23 m)	yes	AM	38 (3 m); 5 (23 m)	del/del	-	CM; CNSM
36	F	N (9 m); R (6 y)	9 y	NIV <16 h	yes	AM; HC (5 m); Sit (16 m)	20; HFMSE: 6	del/del	-	none
37	F	N (9 m)	9 y	Tracheo (1 m)	yes	None	0	del/del	-	CM
Treated type 0 international										
38	F	R (7 d)	6 m	Tracheo (2 m)	yes	None	11 (birth); 31 (6 m)	del/del	-	CM
39	F	N (16 d); OA (3.5 m)	6.7 y	Tracheo (2 m)	yes	HC (15 m); Sit (25 m)	14 (birth); 22 (81 m)	del/del	-	Preterm 36 + 2; CNSM; CM
Type 1.1/1 a (Italian)										
40	M	no	3 m	-	yes	None	4 (birth)	del/c.*3+1G>C,p. ^{2,19}	-	-
41	M	N (4.3 y); R 4.9 y	12 y	Tracheo (12 m)	yes	None	-	del/del	-	-
Type 1.1/1 a (international)										
42	F	no	Died (23 d)	NIV >16 h	yes	None	-	del/del	-	Preterm 36; CM
43	F	no	3.4 y	Tracheo (9 m)	yes	None	0 (41 m)	del/del	-	CM
44	M	N (5 y)	10 y	Tracheo (3 m)	yes	None	2 (10 y)	del/del	-	-
45	F	no	Died at 3 m	NIV >16 h	yes	None	6 (birth)	del/del	-	-
Intermediate (Italian)										
46	F	N (8 y); R (10.6 y)	15 y	NIV <16 h	yes	None	11 (12 y); 12 (13 y); 12 (14 y); 11 (15 y)	del/del	-	-
Intermediate (international)										
47	F	R (2 m)	3 m	Tracheo (2 m)	yes	None	4 (3 m)	del/del	-	CM
48	M	no	Died at 20 m	Tracheo (1 m)	yes	None	0 (birth); 0 (20 m)	del/del	-	CM
49	M	no	Died at 2 y	Tracheo (1 m)	yes	None	0 (24 m)	del/del	-	CM; CNSM
50	M	12 m (N)	Died at 4 y	Tracheo (1 m)	yes	None	0 (4 y)	del/del	-	CM; CNSM

“AM” antigravity movements; “C” Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); “CM” cardiac malformations; “CNSM”; Central Nervous System malformations; “d” day; “HC” head control; “ID” intellectual disability; “m” month; “N” Nusinersen; “NIV” non-invasive ventilation; “NG/G tube” naso-gastric/gastric tube feeding; “OA” Onasemnogene ABERPAROVEC; “polim” polymorphism; “R” Risdiplam; “Sit” sitting control; “w” week; “y” year. ¹⁹Previously reported as c.888+1G>C.

Table 1: Individual characteristics of the neonatal onset cohort.

details of the phenotypic spectrum. Our results show that the most frequent phenotype is the severe form of SMA, type 0, but that milder forms, including type 3, are not exceptional.

The first step was to define the spectrum of clinical phenotypes associated with a single copy of *SMN2* at a national level by collecting information from all the 36 specialised centres for SMA in Italy. Most individuals had neonatal onset (71%) with type 0 SMA being the most frequent phenotype, accounting for 57% of the whole cohort. Another individual had an intermediate phenotype between type 0 and type 1 as he had some prenatal signs (reduced foetal movements and cardiac malformation), but no contractures. Two other individuals (9%) exhibited type 1.1 phenotype, also with limited survival. All these individuals had the most frequent genotype, the homozygous deletions of *SMN1*. The remaining individuals had onset after the neonatal period, ranging from milder type 1 subtypes (SMA type 1.5) to later onset and even milder phenotypes. The

smaller group of individuals with milder phenotypes were either compound heterozygotes for *SMN1* deletion and small variants, or carried the positive c.859G>C, p(Gly287Arg) variant in *SMN2*. Our data confirm and expand previous anecdotal cases reporting the association between these two variants (c.859G>C or c.835-44A>G) and milder phenotypes.^{29,30}

As a single *SMN2* copy is a relatively uncommon finding, data from the Italian network were integrated with those obtained as part of a large international collaboration which showed a similar distribution of phenotypic severity.

The cumulative data in the overall cohort confirm that for the genotype characterised by the homozygous deletion of *SMN1*, a single *SMN2* copy without detectable sequence variants is generally associated with a severe phenotype (98%) with prenatal/neonatal onset, most frequently a type 0 phenotype. We did not observe obvious molecular distinction between type 0 and type 1.1 individuals, but these results should be interpreted

ID	Sex	DMT treatment	Last follow up	Respiratory management	NG/G Tube	Early movements/milestones	CHOP	Genotype		Additional features
								SMN1	SMN2	
Later onset—type 1.5 (Italian)										
51	M	N (2.2 y); OA (4 y); R (6.2 y)	6.6 y	NIV <16 h	No	HC (Unk); Sit (3.5 y)	31 (3.8 y); 37 (5.6 y)	del/c.91dup, p.(Ser31PhefsTer2) ^a	–	MC; ID Acronecrosis
52	F	N (7 y)	12 y	NIV <16 h	yes	None		del/del	–	CM
Later onset—type 2/3 (Italian)										
53	M	OA (17 m)	18 m	–	No	HC (3 m); Sit (6 m)	HFMSE: 40 (17 y)	del/c.821C>T, p.(Thr274Ile)	–	–
54	M	N (29 y)	36 y	–	No	HC (4 m); Sit (7 m)	HFMSE: 25 (36 y)	del/c.389 A>G, p.(Tyr130Cys) ²⁰	–	–
55	M	N (45 y)	51 y	–	no	HC (3 m); Sit (6 m)	–	del/del	c.859G>C,p.(Gly287Arg)	–
56	M	N (46 y)	53 y	–	no	HC (3 m); Sit (6 m)	–	del/del	c.859G>C,p.(Gly287Arg)	–
Later onset—type 2/3 (international)										
57	M	no	36 y	–	no	HC (3 m); Sit (6 m)	–	del/c.460C>T,p.(Gln154Ter) ²¹	–	–
58	M	N (14 y)	17 y	NIV <16 h	no	HC (2 m); Sit (7 m)	–	del/c.5C>G,p.(Ala2Gly) ²¹	–	–
59	M	no	9 y (died)	Tracheo (8 y)	yes	HC (3 m); Sit (8 m)	34	del/c.5C>G,p.(Ala2Gly) ²¹	–	–
60	M	N (11 y)	15 y	Tracheo (8 y)	yes	HC (2 m); Sit (9 m)	29 (4 y)	del/c.5C>G,p.(Ala2Gly) ²¹	–	–
61	F	R (23 y)	25 y	NIV <16 h	no	HC (3 m); Sit (7 m)	43 (22 y)	del/c.5C>G,p.(Ala2Gly) ²¹	–	–
62	F	N (14 y)	18 y	Tracheo (10 y)	yes	HC (2 m); Sit (6 m)	52 (4 y)	del/c.5C>G,p.(Ala2Gly) ²¹	–	–
63	F	no	13 y	–	no	HC (3 m); Sit (7 m)	–	del/c.5C>G,p.(Ala2Gly) ²¹	–	–
64	F	N (36 y); R (37 y)	43 y	NIV <16 h	no	HC (3 m); Sit (6 m)	HFMSE: 0 (43 y)	del/c.834+5G>?,p.? ^b	–	–
65	F	R (52 y)	53 y	NIV <16 h	no	HC (3 m); Sit (6 m)	–	del/c.873 T>C; p.(His291 =) ^c	–	–

^aAM” antigravity movements; “C” Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); “CM” cardiac malformations; “CNSM”; Central Nervous System malformations; “d” day; “HC” head control; “ID” intellectual disability; “m” month; “N” Nusinersen; “NIV” non-invasive ventilation; “NG/G tube” naso-gastric/gastric tube feeding; “OA” Onasemnogene ABERPARVOVEC; “polim” polymorphism; “R” Risdiplam; “Sit” sitting control; “w” week; “y” year. ^bClassified as Pathogenic (Class V ACMG) according to the criteria PVS1, PM2_S, PM3. ^cClassified as Likely pathogenic (Class IV ACMG) according to the criteria PM1, PM2_S, PM3, PM4. ^dClassified as Likely pathogenic (Class IV ACMG) according to the criteria PM1, PM2_S, PM3, PM4.

Table 2: Individual characteristics of the later onset cohort with a single SMN2 copy.

ID	Sex	DMT treatment	Last follow up	Respiratory management	NG/G Tube	Early Movements/milestones	CHOP	Genotype		Additional features
								SMN1	SMN2	
Two SMN2 copies (Italian)										
66	M	OA (1 m)	13 m	NIV <16 h	no	HC (6 m); Sit	4 (birth); 4 (13 m)	del/del	–	CM
67	M	R (Unk)	16 m	NIV <16 h	yes	HC (12 m); Sit (17 m)	30 (16 m)	del/del	–	–
68	M	OA (20 d)	29 m	NIV <16 h	yes	HC (17 m); Sit (23 m)	15 (birth); 46 (29 m)	del/del	–	CM
Two SMN2 copies (international)										
69	M	R (2 m); OA (3 m)	10 m	–	no	HC (4 m)	40 (10 m)	del/del	–	CM
70	M	OA (Unk)	16 m	NIV <16 h	yes	None	19 (birth); 32 (16 m)	del/del	–	CM
71	F	OA (17 d); R (13 m)	2.8 y	NIV <16 h	no	HC (24 m); Sit (26 m)	23 (birth); 52 (2.8 y)	del/del	–	CM
72	M	no	10.5 y	Tracheo (1.5 m)	Yes	None	10 (birth); 4 (10 y)	del/del	–	–

^aAM” antigravity movements; “C” Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); “CM” cardiac malformations; “CNSM”; Central Nervous System malformations; “d” day; “HC” head control; “ID” intellectual disability; “m” month; “N” Nusinersen; “NIV” non-invasive ventilation; “NG/G tube” naso-gastric/gastric tube feeding; “OA” Onasemnogene ABERPARVOVEC; “polim” polymorphism; “R” Risdiplam; “Sit” sitting control; “w” week; “y” year.

Table 3: Characteristics of the more than one SMN2 copies cohort.

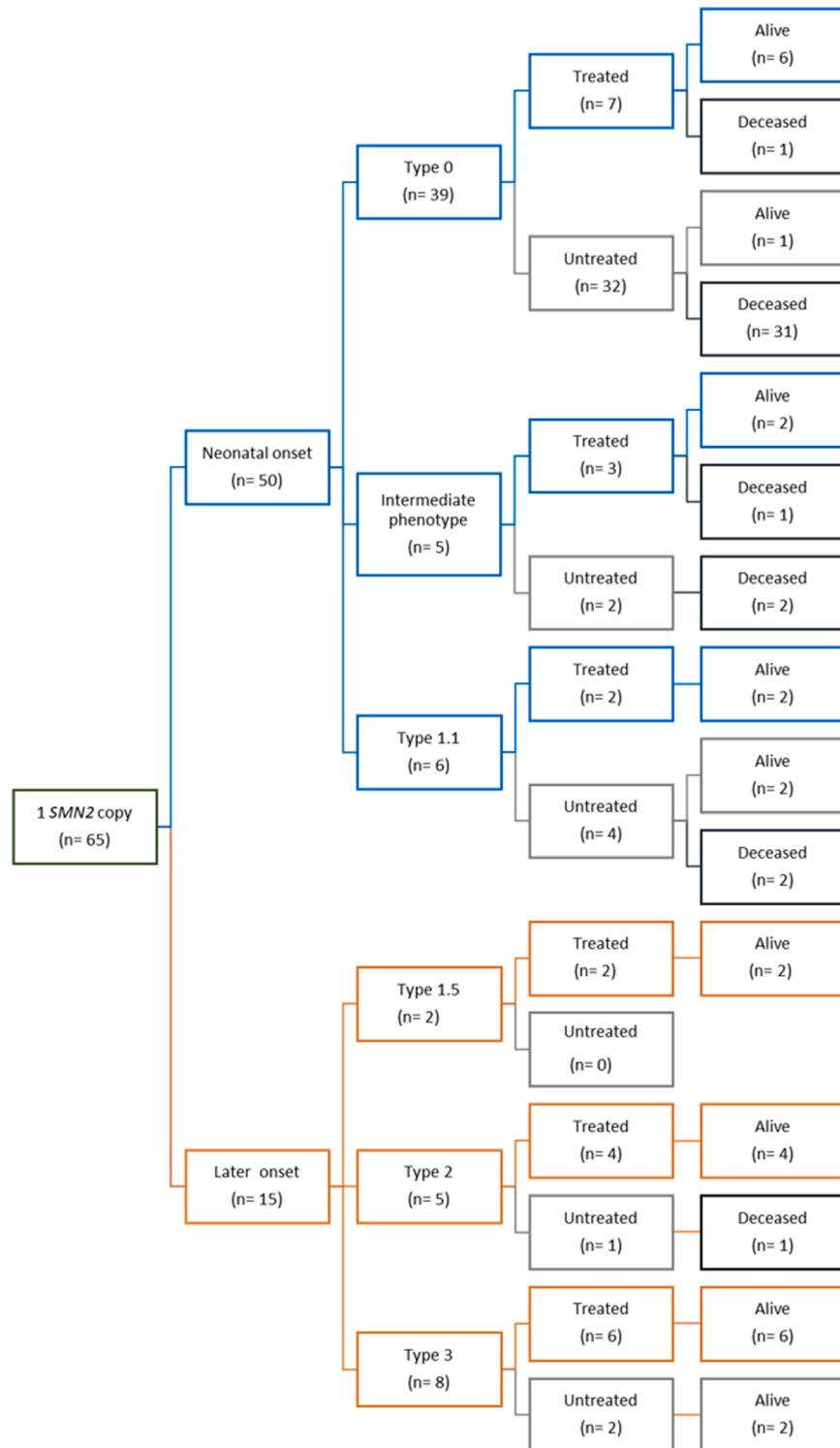


Fig. 2: Flowchart of allocation of individuals with one SMN2 copy into categories, with details on DMT treatment and survival status at last available follow-up. Exact ages at death or last follow-up are reported in [Tables 1-3](#).

with caution because the difference type 0 and type 1.1 or 1A in the literature is not always well established or applied. In this study, when centres were asked to review their cohorts according to more stringent criteria, a small number of infants who had originally been classified as type 1 were found to have contractures and other criteria compatible with a classification of type 0.

A number of individuals had a milder phenotype, and the clinical heterogeneity could be at least partly explained by the presence of mild *SMN1* pathogenic variants or *SMN2* variants, enhancing exon 7 inclusion. As also observed at national level, nearly all the individuals with milder phenotype were compound heterozygotes for deletion of one allele and small variants, or had the c.859G>C, p(Gly287Arg) *SMN2* variant.³¹ Our findings suggest that this variant as well as the c.835-44A>G should be specifically investigated in any infant with one *SMN2* copy who does not present with a classical SMA 0 phenotype.²⁹ An additional methodological consideration is the challenge of accurately determining *SMN2* copy number, which can be affected by technical limitations of the commonly used assays.^{2,30,32}

The need to better understand the full spectrum of phenotypes associated with a single copy of *SMN2* is dictated by the different availability of DMTs in different countries. In many countries the access to DMTs is denied to individuals with a type 0 phenotype, or with one copy of *SMN2*. Even in countries without regulatory restrictions, the number of treated individuals with type 0 or with a single *SMN2* copy reported in the literature is very small, as it has been assumed that because of the severity of the clinical and neurophysiological findings, the chances of efficacy would be very limited.

In our overall cohort the large majority (80%) of the type 1.5 individuals or milder phenotypes had been treated, but only a small proportion (7/39, 18%) of type 0 with a single copy of *SMN2* received treatment. Of the six infants with type 0 phenotype and a single copy of *SMN2* who did not have tracheostomy at the time they received treatment, one died and 3 required tracheostomy. Two of the six achieved head control and independent sitting, and their clinical trajectories were notably different from those untreated both in our cohort and in the literature, in whom the mean survival without tracheostomy was extremely limited. In contrast, treatment in the individual who already had tracheostomy produced small changes. These results are apparently not consistent with the recently reported motor improvement post gene therapy in tracheotomised individuals that however included infants with a wider range of *SMN2* copies.² These data should be considered cautiously given the small numbers of individuals and the potential selection bias.

Another factor to be considered for infants with type 0 SMA is the possible heterogeneity of the genetic

background. Following reports of anecdotal cases of typical type 0 phenotype associated with two *SMN2* copies with slightly milder phenotypes, we also investigated the frequency and the outcome of such association both at national and international level. We identified six individuals who fulfilled clinical criteria for type 0, with contractures and often other prenatal signs and severe neonatal involvement, who were found to have two *SMN2* copies. Interestingly, all of them were treated and all survived, acquiring some milestones and without need for continuous ventilation. In these individuals the outcome was not dissimilar from that observed in other individuals with two *SMN2* copies and a type 1.1 phenotype who, despite generally being less responsive to treatment than type 1.5 and 1.9 phenotypes, still have increased survival and small improvements on the functional scales.³³ These results raise the clinical and ethical issue of whether in the healthcare systems in which individuals with type 0 SMA are excluded from receiving DMTs, clinicians and families should be given the opportunity to discuss possible treatments, even if the expectations of efficacy are realistically limited.

This consideration may be particularly relevant in individuals who present with less severe clinical signs or carry genetic background associated with partial functional rescue, such as mild *SMN1* small variants and/or *SMN2* variants enhancing exon 7 inclusion (see [Tables 1–2](#)). The presence of such genotypes may contribute to improved SMN protein production and partially mitigate disease severity, further supporting the need for in depth molecular characterisation in guiding counselling and therapeutic decisions.

This study reinforces the growing recognition that motor neuron degeneration in the most severe SMA cases begins in utero, often well before birth.³⁴ Recently, several prenatal findings that may also be detected later at birth or soon after, have been added to the list of Human Phenotype Ontology (HPOs) to better recognise type 0 affected fetuses.³⁵ This understanding raises the critical question of whether prenatal treatment, currently being explored in preclinical and early-phase clinical studies,³⁶ could offer meaningful neuroprotection and improved outcomes for fetuses with genetically confirmed SMA and early clinical signs. The expanding implementation of pre-conceptional/prenatal genetic testing for SMA and the possible identification of a foetus carrying a single *SMN2* copy raises complex counselling challenges as there is limited experience in infants with one *SMN2* copy, although increasing evidence supports the efficacy of DMTs initiated in utero or before term age.³⁷

In conclusion, our data provide detailed information on the spectrum of phenotypes associated with a single *SMN2* copy and on phenotype–genotype association. The presence of some mild *SMN1* variants or known *SMN2* positive variants, may have a mitigating effect on

the severity of the phenotype suggesting that mild phenotypes should prompt the search for *SMN2* variants that may positively affect the phenotypic outcome. Our data also underscore the need to refine the criteria for classifying these individuals. While type 0 appears to be the most frequent phenotype, the boundaries between types 0 and 1.1 appear increasingly fluid, or the concept of a strict categorical classification may need to be replaced by a continuum model, considering genotype, prenatal indicators and early clinical signs. Although the series of individuals in the present paper is so far the largest reported in the literature, our study was limited by its retrospective nature that introduces a risk of incomplete or non-uniform reporting, particularly for prenatal indicators such as foetal movements or polyhydramnios, which may have been inconsistently documented across centres or over time. Similarly, the search for modifier variants was also not systematically assessed across centres. Further prospective studies also including neurophysiological and biochemical biomarkers, and structured assessments aimed at better characterising the degree of multi-systemic involvement, would help to better characterise the spectrum and the overlap of individual phenotypes and their impact on disease progression and survival. In our global cohort details on the use of respiratory assessment tools, ventilatory interfaces and gastrostomy placement were not uniformly collected, particularly in historical cases. Considering the relatively large time frame, it is likely that the decision-making processes have progressively changed in response to advances in care recommendations over the last decade. Prospective studies will also help to better understand sustained functional gains, quality of life, and survival, also in relation to more recent care recommendations.

Despite the effort to collect data from a large cohort, some questions remain unsolved. Our data suggest that treatment with the available DMTs appears to have no obvious effect in the most severe phenotypes with limited evidence of efficacy in those treated earlier, but caution is needed given small numbers. A more individualised, flexible approach, focussing on a combination of clinical features and precise genotyping, including modifier variants, may help to better define evidence-based frameworks for treatment eligibility and timing in the clinically and ethically complex landscape of the most severe SMA presentations.

Contributors

GC and AC equally contributed as first authors of the manuscript and performed material preparation, data collection and analysis. EM, MP, DT, AC and GC wrote the first draft of the manuscript. GC and EM accessed and verified the underlying data. All authors contributed to the data collection, study conception and design and commented on previous version of the manuscript. All authors read and approved the final manuscript.

Data sharing statement

De-identified individual participant data supporting the findings of this study are provided within the tables of the published article. Additional

individual-level data are not publicly available due to restrictions related to informed consent and data protection regulations but may be made available upon reasonable request to the corresponding author following publication. No custom code or specialised software was used for data processing or analysis beyond standard statistical tools.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2026.103931>.

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